

**NONPUBLICATION AND PUBLICATION BIAS IN CLINICAL TRIALS IN CANADA:
A QUALITATIVE INTERVIEW STUDY**

by

Richard Lee Morrow

B.A., McGill University, 1995

M.A., University of Victoria, 2005

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES
(Interdisciplinary Studies)

[Anesthesiology, Pharmacology & Therapeutics; Population and Public Health; Sociology]

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

February 2022

© Richard Lee Morrow, 2022

The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, the dissertation entitled:

Nonpublication and publication bias in clinical trials in Canada: a qualitative study

submitted by Richard Lee Morrow in partial fulfillment of the requirements for

the degree of Doctor of Philosophy

in Interdisciplinary Studies

Examining Committee:

Colin Dormuth, Associate Professor, Anesthesiology, Pharmacology & Therapeutics, UBC
Co-supervisor

Barbara Mintzes, Associate Professor, Charles Perkins Centre and School of Pharmacy,
University of Sydney; Affiliate Associate Professor, School of Population and Public Health,
UBC
Co-supervisor

Garry Gray, Associate Professor, Sociology, University of Victoria
Supervisory Committee Member

Mieke Koehoorn, Professor and Associate Director, Research, School of Population and
Public Health, UBC
University Examiner

Susan Cox, Associate Professor and Director, PhD and MSc Programs, School of Population
and Public Health, UBC
University Examiner

Additional Supervisory Committee Members:

Michael Law, Professor, Centre for Health Services and Policy Research, School of Population
and Public Health, UBC
Supervisory Committee Member

Abstract

Background: Selective publication of clinical trials is common and leads to publication bias, but factors contributing to selective publication are not well understood. It is also unclear whether trialists believe they have a duty to trial participants to report their research.

Objective: To understand (i) whether and how industry sponsors of clinical trials influence decisions to report trial results, (ii) factors contributing to nonpublication and publication bias, and (iii) how the experiences and views of trial participants, trial investigators, and others connected to clinical trial research relate to whether researchers have a duty to trial participants to report research findings.

Design: Qualitative interview study.

Participants: 34 participants including 17 clinical trial investigators, 1 clinical research coordinator, 3 research administrators, 3 research ethics board members, and 10 clinical trial participants.

Setting: Semistructured interviews conducted in person or by telephone with participants from Alberta, British Columbia, and Ontario, Canada.

Analysis: Data analysis was informed by grounded theory, including coding of interview transcripts, memo-writing, and developing key themes.

Results: Industry sponsors may influence whether clinical trials are reported through stopping trials early and not reporting results, ownership and control of data, clinical trial agreements which do not fully protect an investigator's right to publish, control of internal company trials, and funding dependency. While companies have a commercial incentive to selectively report trials, other incentives within clinical research also appear to favour publication of positive over negative trials. Positive findings are perceived to be easier to publish, to help investigator's

ability to access industry and nonindustry research funding, and to be rewarded by research institutions in hiring, promotion and recognition. Interviews suggested that when participants enter a trial, there is often an implicit understanding between researchers and participants involving a responsibility to report results. Accounts of trial investigators suggested reporting research results is a necessary part of honouring informed consent.

Conclusions: While clinical trial reporting is valued in Canada, selective reporting of clinical trials arises for a variety of reasons. Policy to promote full reporting of trials may be strengthened by recognizing factors that contribute to nonpublication and publication bias.

Lay Summary

Clinical trials are important for understanding treatment safety and effectiveness, but results of trials are often not published. This study aimed to understand the reasons that clinical trial results are not reported and to understand views about reporting of clinical trial results. It involved interviews with trial investigators, a clinical research coordinator, research administrators, research ethics board members, and trial participants. One of our findings is that companies have a weaker incentive to publish trials that are unfavourable to their products, and they may influence whether a trial is reported in various ways. Another finding is that researchers may have a greater interest in publishing trials with positive results, because these trials may be more likely to lead to research funding and to career advancement and recognition. Interviews suggested that when participants enter a trial, there is often an understanding between researchers and participants involving a responsibility to report results.

Preface

This research study was conceived and designed by the PhD candidate and was not part of an existing research program. PhD committee members provided feedback on the design and methods of the study. The PhD candidate organized the recruitment of participants, conducted the research interviews, and carried out qualitative coding of data and analysis. Most recruitment activities were carried out by the PhD candidate. Recruitment of clinical trial participants to participate in interviews also involved the assistance of clinical research coordinators in British Columbia and Alberta, who sought consent from past trial participant for the PhD candidate to contact them about participation in interviews. In addition, a transcriber was hired to produce the interview transcripts that were used for analysis, based on audio recordings of the interviews.

The PhD candidate drafted and edited all components of the thesis, including 3 chapters which were prepared in manuscript form and are intended to be published as journal articles (Chapters 3, 4 and 5). A version of Chapter 3 has been published (Morrow RL, Mintzes B, Gray G, Law MR, Garrison S, Dormuth CR. Industry Sponsor Influence in Clinical Trial Reporting in Canada: A Qualitative Interview Study. *Clinical therapeutics*. 2021. doi: <https://dx.doi.org/10.1016/j.clinthera.2021.11.019>). Members of the PhD committee provided feedback for interpretation of the research and revision of the manuscripts and all parts of this thesis. In addition, Dr. Scott Garrison, a clinical trial investigator and associate professor in Family Medicine at the University of Alberta, provided feedback regarding interpretation and revision of the draft manuscripts from this study.

The study received ethics approval from the University of British Columbia Behavioural Research Ethics Board (H18-03458) and the University of Alberta Health Research Ethics Board (Pro00096201). All participants provided informed consent.

Table of Contents

Abstract	iii
Lay Summary	v
Preface	vi
Table of Contents	vii
List of Tables	x
List of Abbreviations	xi
Acknowledgements	xiii
Chapter 1: Introduction	1
1.1 Background and rationale	1
1.2 Objectives	4
1.3 Study design and methods	5
1.4 Terminology: describing trials as <i>positive</i> or <i>negative</i>	7
1.5 Thesis organization	8
Chapter 2: Literature review	10
2.1 Introduction.....	10
2.2 Industry influence in clinical trial reporting	13
2.3 Factors contributing to nonpublication and publication bias	20
2.4 Dissemination of research findings as a duty to clinical trial participants	28
2.5 Policies to address nonpublication and publication bias.....	30
2.6 Summary	43
Chapter 3: Industry sponsor influence in clinical trial reporting in Canada	46
3.1 Introduction.....	46

3.2	Methods.....	48
3.3	Results.....	52
3.4	Discussion.....	63
Chapter 4: Factors relating to nonpublication and publication bias in clinical trials in		
Canada71		
4.1	Introduction.....	71
4.2	Methods.....	72
4.3	Results.....	75
4.4	Discussion.....	82
Chapter 5: Reporting clinical trial findings as an ethical responsibility to research		
participants.....88		
5.1	Introduction.....	88
5.2	Methods.....	89
5.3	Results.....	91
5.4	Discussion.....	99
Chapter 6: Clinical trial transparency in the context of strategic interests and power104		
6.1	Strategic interests and power relating to clinical trial transparency	104
6.2	Dynamics of changing policy and practices relating to trial transparency	111
6.3	Ethical implications	113
6.4	Transparency of individual patient data and clinical study reports	114
6.5	Summary.....	116
Chapter 7: Discussion and conclusions117		
7.1	Summary of key findings and contributions.....	118

7.2	Policy implications.....	123
7.3	Importance of reporting results in academic journals and trial registries	126
7.4	Strengths and limitations of the study.....	127
7.5	Future research.....	128
7.6	Conclusions.....	129
References.....		139
Appendices.....		164
Appendix A Interview guides		164
A.1	Interview guide for clinical trial investigators	164
A.2	Interview guide for research administrators	167
A.3	Interview guide for clinical research ethics board members	171
A.4	Interview guide for clinical trial participants.....	174
Appendix B Questions sent to Canadian Institutes of Health Research and replies.....		176

List of Tables

Table 1. Types of interview participants and inclusion criteria.....	132
Table 2. Interview participant characteristics	133
Table 3. Interests, power, and actions and omissions of actors connected to clinical trial research	135
Table 4. Summary of key contributions of this study.....	137
Table 5. Initial questions and assessments sent to the Canadian Institutes of Health Research and replies	177
Table 6. Follow-up questions sent to the Canadian Institutes of Health Research and replies ..	187

List of Abbreviations

AAG	<i>Canadian Institutes of Health Research (CIHR) Application Administration Guide</i>
ATUF	authority to use funds
CI	confidence interval
CIHR	Canadian Institutes of Health Research
CONSORT	Consolidated Standards of Reporting Trials
CSR	clinical study report
CTA	clinical trial agreement
CV	curriculum vitae
DORA	San Francisco Declaration on Research Assessment
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUCTR	European Union Clinical Trials Register
FDA	Food and Drug Administration
FO	funding opportunity
ICMJE	International Committee of Medical Journal Editors
IQR	interquartile range
NIH	National Institutes of Health
NIHR	National Institutes of Health Research
NPI	nominated principal investigator
NSERC	Natural Sciences and Engineering Research Council

OR	odds ratio
RCT	randomized controlled trial
REB	research ethics board
RCR Framework	<i>Tri-Agency Framework: Responsible Conduct of Research (2016)</i>
SSHRC	Social Sciences and Humanities Research Council
SSRIs	selective serotonin reuptake inhibitors
SBD	Summary Basis of Decision
SD	standard deviation
SRQR	Standards for Reporting Qualitative Research
TAGFA	<i>Tri-Agency Guide on Financial Administration</i>
TCPS2	<i>Tri-council policy statement: ethical conduct for research involving humans</i>
US	United States
WHO	World Health Organization

Acknowledgements

I would like to express my deep appreciation to my co-supervisors, Dr. Colin Dormuth and Dr. Barbara Mintzes, for their support and guidance. Many thanks as well to Dr. Garry Gray and Dr. Michael Law for their timely and expert advice. I would also like to thank Dr. Scott Garrison for his support for this research.

I would like to acknowledge that this work was supported by unrestricted funds granted to the University of British Columbia from the British Columbia Ministry of Health.

Thank you to my colleagues at the Therapeutics Initiative for their support and inspiration. Special thanks to Dr. James Wright and Dr. Ken Bassett for their support for my studies and research, and Alan Cassels for discussing my preliminary research ideas for what became this project.

I would like to express my gratitude to everyone who was willing to take part in this study and to discuss their views and experiences, without whom this research would not have been possible. In addition, I would like to thank the clinical research coordinators who helped with recruitment for the study by seeking consent from past trial participants for me to contact them about the study, and their colleagues who were supportive of this research.

Finally, heartfelt thanks to Stacy Chappel and Felix Morrow for their constant support and encouragement.

Chapter 1: Introduction

Selective publication of clinical trials is common, and this makes it more difficult for researchers, physicians, and others to know which treatments are safe and effective.¹⁻³ This study investigated nonpublication and publication bias in Canada through qualitative interviews with trial investigators, trial participants, and others connected to trial research. This chapter describes the background and rationale for the research study, the study's objectives, the study design and methods, and how the thesis is organized.

1.1 Background and rationale

The problem of nonpublication in medical research has been apparent for over 30 years,⁴⁻⁶ and has been well-documented in many areas of medicine.⁷⁻¹¹ A systematic review indicated approximately 40% of randomized controlled trials included in trial registries were not published as journal articles, based on studies of nonpublication which assessed whether studies were published a minimum of 2 years from study completion.³ Similarly, other systematic reviews suggest many clinical and biomedical studies are not published.^{1,2,12-15}

Selective publication of medical research has been shown to result in publication bias, which occurs when positive studies are more likely to be published than negative studies.¹⁻³ When publication bias is assessed, "positive" studies may be defined as those with results favourable toward the experimental treatment or those with results that are statistically significant. Publication bias in both senses occurs in biomedical research.¹⁻³ This was illustrated in a recent systematic review, which found clinical studies were more likely to be published if they had favourable results for the test treatment (odds ratio [OR], 2.04; 95% confidence interval [CI], 1.62-2.57) or results that were statistically significant (OR, 2.07; 95% CI, 1.52-2.81).¹

When medical studies are published selectively, this may undermine clinical decision making.^{16,17} This is illustrated by an analysis of antidepressant trials which found the published literature overstated the effect size of selective serotonin reuptake inhibitors (SSRIs) and other antidepressants.¹⁸ As a result, physicians lacked a realistic assessment of these medications when treating patients with depression. Nonpublication may also lead to widespread harms.¹⁷ It is estimated that routine prescribing of anti-arrhythmic medications to heart attack patients led to over 100,000 premature deaths, but this loss of life may have been lessened or averted if a trial showing the mortality risk associated with the anti-arrhythmic lorcaïnide had been published after it was completed in 1980 rather than more than a decade later.^{19,20} In addition, investments in health research are arguably wasted when research findings are inaccessible due to nonpublication.^{17,21}

Industry sponsors provide funding for a substantial proportion of clinical trial research in Canada and internationally.²² While industry sponsorship of trials provides many benefits, sponsors may have a commercial incentive to selectively publish trials which favour their products.²³ This is illustrated by cases where internal documents have indicated the intention to suppress findings.²⁴⁻²⁷ For example, internal documents from Parke-Davis revealed the intention to preferentially publish positive findings about gabapentin.²⁷ While the position of sponsor may provide companies with the ability to influence clinical trial reporting, the mechanisms through which industry sponsors may influence whether trials are reported are not well understood.

Various factors likely contribute to nonpublication and publication bias in trial research. Randomized and later phase trials are more likely to be published,^{1,2} while trials stopped prematurely are less likely to be published.²⁸⁻³³ Journal reviewers may favour positive trials.³⁴ When surveyed, reasons given by investigators for not publishing clinical trials included

unimportant results, incomplete study, negative results, expectation of journal rejection, and lack of permission from sponsor to publish.^{14,35} However, common reasons given for nonpublication, such as lack of time and/or resources and low priority, are somewhat difficult to interpret.^{14,35} While survey studies provide valuable information about a wide range of contributing factors, their findings are somewhat ambiguous and do not provide an in-depth account of investigator experiences of clinical trial reporting.

Clinical trial participants take part in trials for a variety of reasons, including access to experimental treatment and a desire to help others.³⁶⁻³⁹ While trial participants may not receive a direct benefit from a trial, they may reasonably expect society to benefit through a trial's contribution to medical knowledge.^{19,40-43} When clinical trial results are not reported in a journal or trial registry, their contribution to knowledge is diminished. For this reason, some researchers have suggested nonpublication betrays trial participants or breaks an implicit contract between trialists and trial participants.^{19,40-43} However, it is unclear to what extent trial participants value publication of trial results or whether trial investigators believe they have a responsibility to trial participants to report their research.

The introduction of trial registries and the adoption of regulatory requirements to report the results of clinical trials within trial registries have increased transparency, although many trials are still not reported and Canada has yet to introduce regulatory requirements to report trial findings.^{44,45} While registries and regulatory requirements are important, policies of research institutions, funders, and research ethics boards (REBs) are also relevant to nonpublication and publication bias as these entities help define the context in which clinical trial research is conducted and reported.^{17,46-48} As a multifaceted approach is likely needed to address

nonpublication, it is important consider policy actions that might be taken regulators, research institutions, funders, and REBs to promote full reporting of trials.

Nonpublication and publication bias in clinical trial research are both important to consider. The term nonpublication refers to not publishing the summary results of a clinical trial. As described above, publication bias refers to the more frequent publication of studies with results favourable to the experimental treatment or results that are statistically significant. When the published literature on clinical trials is characterized by publication bias, it misrepresents the true benefits and risks of treatments, which is clearly undesirable. However, even nonpublication in the absence of publication bias can be problematic. First, when clinical trials of a new treatment remain unpublished, meta-analyses relying on data from published studies might lack statistical power that could provide insights about treatment effects. Second, nonpublication in the absence of publication bias may also prevent the scientific community from learning useful information from a trial, such as information relevant to the safety profile of a drug or drugs in the same class. As both nonpublication and publication bias are important phenomena in clinical trial research, both will be examined in this study.

1.2 Objectives

This study investigated clinical trial reporting in Canada using a qualitative research design. The primary objectives of the study were as follows:

- (i) To understand whether and how industry sponsors of clinical trials influence decisions to report trial results.
- (ii) To understand factors contributing to nonpublication and publication bias in clinical trials in Canada.

- (iii) To understand how the experiences and views of trial participants, trial investigators, and others connected to clinical trial research relate to whether researchers have a duty to trial participants to report research findings.

In addition, the study had the following secondary objective:

- (iv) To identify implications of the study's findings for policy to address nonpublication and publication bias in clinical trial research.

1.3 Study design and methods

This study used qualitative research methods which involved semistructured interviews to collect data on the experiences and views of clinical trial participants, trial investigators, a clinical research coordinator, research administrators and REB members. The study used a grounded theory approach to data collection and analysis.^{49,50} As this methodology may be used to understand social processes, it was well-suited for investigating the range of factors that might be related to nonpublication and publication bias.^{49,51} This approach involved iteratively conducting data collection and analysis during the study, analyzing actions and processes, and comparing incidents and statements from the same or different interviews.⁴⁹

We identified participants primarily through purposive sampling, including trial investigators from various medical specialties, trial participants from trials of a range of treatments, and participants from different provinces. This was complemented by snowball sampling to gain referrals to additional trial investigators and REB members. Interview participants were recruited based on the inclusion criteria shown in **Table 1**. The University of British Columbia Behavioural Research Ethics Board (H18-03458) and the University of Alberta Health Research

Ethics Board (Pro00096201) approved the study, and all interview participants provided informed consent.

While the semistructured format of interviews provided flexibility for exploring questions arising during the course of interviews, interview guides were developed for each type of participant. (**Appendix A**) Questions aimed to elicit information relevant to the study objectives described above. Specifically, interview guides included questions regarding trial participant experiences in taking part in trials and trial investigator experiences in conducting trials, including any unpublished trials. In addition, interview questions prepared for research administrators covered policy and experiences relating to clinical trial reporting, while questions for REB members highlighted policy and experiences regarding ethical review of clinical trials in relation to reporting clinical trial findings.

Interviews included primary interviews (n=34) of approximately 45 to 60 minutes in length and in some cases follow-up interviews (n=4) which lasted approximately 20 minutes. RM interviewed each participant individually with the exception of an interview involving a trial investigator and clinical research coordinator who worked in the same office. Additional interviews were conducted until data allowed for an in-depth analysis addressing the study objectives described in the preceding section. Interview participants from the provinces of Alberta, British Columbia and Ontario took part in the study.

In May and June 2021, RM contacted Canadian Institutes of Health Research (CIHR) by email to clarify aspects of the agency's policies. This included requirements for grant recipients to report clinical trial results, guidelines for assessment of researchers applying for grants to conduct clinical trials, and policy on use of grant funds provided for a clinical trial beyond the

initially planned end date of the grant. (Questions sent to CIHR and responses received are included in **Appendix B**.)

Interviews were audio-recorded and transcribed for analysis. Interview transcripts were analyzed using ATLAS.ti qualitative software, version 8. RM conducted the data analysis, which involved initial coding with sensitivity to social processes, focused coding to retain and develop the most important codes, memo-writing to develop key themes, and developing a more theoretical interpretation based on these themes.⁴⁹ Triangulation of data from different types of participants was used to strengthen the reliability of the study.⁵²

1.4 Terminology: describing trials as *positive* or *negative*

This thesis has adopted the terminology of referring to trials as *positive* or *negative* throughout this paper, both for readability and to reflect the way that interview participants commonly referred to trials. Interview participants primarily spoke about trials of investigational drugs or trials of drugs for investigational uses. In this context, it is usually implicit that a positive trial is one with a result for a primary outcome that is statistically significant and favourable for the experimental treatment rather than a placebo or a comparison treatment, while trials with a nonsignificant result for the primary outcome or a significant result which is not favourable for the experimental treatment would be considered negative. In the case of a noninferiority trial, a positive trial would mean one with no statistically significant difference in between the experimental and control treatment, and trials with a significant result in favour of the control would be negative. Except when otherwise specified, the reader can assume the above definitions apply when positive and negative results or trials are mentioned in this thesis.

In the literature, *positive* trials have been defined as trials with statistically significant results or trials with statistically significant results favourable toward the test treatment.^{1,2} Preferential publication of positive trials in either sense represents publication bias and has been demonstrated in systematic reviews to occur biomedical studies.^{1,2} When noninferiority trials are considered, a positive trial might be defined to include both trials with significant results in favour of the experimental intervention and trials with no statistically significant difference between the experimental and control intervention.⁵³ While this thesis has referred to nonpositive trials as *negative* trials to reflect the language used by interview participants, a variety of terms has been used in the literature. Some authors have divided nonpositive studies into *nonsignificant* and *significant negative*, *null* and *negative*, or *neutral* and *negative*.^{2,53}

Although this thesis has referred to trials as *positive* and *negative*, this is not intended to communicate or perpetuate a value judgement regarding these types of trials. On the contrary, the consequences of selective publication and value of full reporting of trial results have been highlighted throughout. As one author has reflected, the term “negative study” is unfortunate, because “a well-conducted study is a positive contribution to science.”⁴¹ It is possible that the terms we use to refer to clinical trials with various types of results will evolve as the culture of clinical trial reporting changes.

1.5 Thesis organization

This thesis is organized into 7 chapters, including this introductory chapter. Chapter 2 presents a narrative review of literature on clinical trial reporting most relevant to this study.

While the research conducted for this thesis represents a single qualitative study, it was developed into 3 manuscripts corresponding to study objectives 1 to 3 described above. These

manuscripts are presented in Chapters 3 to 5. Chapter 3 reports on industry influence in clinical trial reporting, and Chapter 4 reports on other factors related to nonpublication and publication bias in clinical trials in Canada. While these chapters reflect interviews with all participants, they draw primarily on interviews with trial investigators and others involved in the conduct, administration or ethical review of clinical trials. The topic of Chapter 5 is reporting clinical trial findings as an ethical responsibility to research participants. This chapter draws more directly from interviews with clinical trial participants, as well as interviews with trial investigators and others. The manuscripts presented in Chapters 3 to 5 each discuss policy implications of the relevant study findings, which corresponds to study objective 4 described above.

Building on the themes presented in Chapters 3 to 5, Chapter 6 provides a consideration of clinical trial transparency in the context of strategic interests and power. As the concluding chapter, Chapter 7 highlights key findings, summarizes policy implications, describes strengths and limitations of the study, and outlines implications for future research. Overall, this thesis presents an investigation of industry sponsor influence and other factors which may contribute to nonpublication and publication bias in clinical trial research in Canada, and some of the ethical implications of not reporting clinical trial findings.

Chapter 2: Literature review

2.1 Introduction

This chapter provides a narrative review of literature on clinical trial reporting. The introductory section provides background on the frequency and consequences of nonpublication and publication bias in biomedical research. The three sections following the introduction each summarize literature corresponding to topics of later chapters of this dissertation, including industry influence in clinical trial reporting, other factors contributing to nonpublication of clinical trials, and the dissemination of research findings as a duty to clinical trial participants. The subsequent section provides a review of policies to address nonpublication and publication bias. The chapter concludes with a section highlighting key points from the chapter and gaps in the literature.

Frequency of nonpublication and publication bias

Clinical trials are important for developing new treatments and providing the best medical care. However, clinical trials and other biomedical studies are often not published or only published after a considerable delay.^{1-3,12-15} A recent systematic review included 85 reports which assessed whether clinical studies were published during an average follow-up time of 4.6 years from study completion.¹ It found an average of 52% (standard deviation [SD], 18.9) of clinical studies were published in journals. Another systematic review analyzed 39 studies of nonpublication with a minimum follow-up time of 24 months after study completion to determine publication status.³ An estimated 54.2% (95% confidence interval [CI], 42.0-65.9) of studies included in trial registries were published as journal articles, and 60.3% (95% CI, 45.4-73.6) of randomized controlled trials included in trial registries were published.

Due to selective publication, the medical literature is characterized by publication bias.¹⁻³ As described in chapter 1, publication bias occurs when studies with positive findings are more likely to be published than studies with negative findings, where “positive” findings may refer to results that are favourable toward the experimental treatment or results that are statistically significant. A systematic review of reports of clinical studies found positive studies were considerably more likely to be published, whether this was defined as favourable results (OR, 2.04; 95% CI, 1.62-2.57) or statistically significant results (OR, 2.07; 95% CI, 1.52-2.81).¹ Another systematic review, including studies of nonpublication evaluating the publication status of studies approved by REBs in any country, found that studies with significant results were more likely to be published (OR, 2.8; 95% CI, 2.2-3.5).³ It also found that studies which had favourable results may be more likely to be published (OR, 3.1; 95% CI, 0.9-11.0), although this finding was based on only two studies of nonpublication and was nonsignificant. Similarly, a systematic review of cohorts of biomedical abstracts found that randomized or controlled trials were more likely to be published if they had favourable or significant findings.² In addition, positive research findings are also published sooner on average than negative findings of clinical or other biomedical research.^{3,12}

Consequences of nonpublication and publication bias

Nonpublication and publication bias in medical research undermine our understanding of treatment efficacy and safety, which may affect clinical decision making.^{17,18,54} The case of selective serotonin reuptake inhibitors (SSRIs) provides an example of how publication bias may distort patient care. An analysis of US Food and Drug Administration (FDA) reviews of 12 antidepressant drugs between 1987 and 2004 showed that most trials with positive results for

prespecified primary outcomes were published, whereas typically trials with negative findings were either not published or were published in a way that represented a positive result.¹⁸ The published literature exaggerated the effect size of SSRIs and other antidepressants, in comparison to the effect size calculated based on both published and unpublished results.¹⁸ Physicians prescribed SSRIs widely for mild-to-moderate depression based in part on the published evidence, but meta-analyses including unpublished trials suggest this class of medications may have little or no efficacy for treatment of depression of mild-to-moderate severity.^{26,55,56}

Nonpublication of clinical trials has contributed to harms related to several types of drug therapy, including the type 2 diabetes drug rosiglitazone and the monoclonal antibody TGN1412.¹⁷ Many trials of rosiglitazone were not published, and the drug's increased risk of heart attack only became publicly known after the May 2007 publication of a meta-analysis which included data from numerous unpublished trials.^{17,57} In July 2007, FDA scientists estimated rosiglitazone had been associated with 83,000 excess heart attacks since entering the market in 1999.⁵⁸ The case of the monoclonal antibody TGN1412 provides a cautionary tale on reporting of phase 1 trials.¹⁷ The six healthy volunteers who participated in this phase 1 trial in March 2006 developed a cytokine release syndrome with multi-organ failure after receiving the drug intravenously, although each survived due to medical treatment.⁵⁹ However, if an earlier trial of a similar antibody had been published, it may have helped avoid this trial from proceeding.¹⁹

The nonpublication of medical research may also lead to waste of both research and health care resources.^{17,21} Some studies have highlighted the proportion of publicly-funded research projects which fail to produce publications.^{60,61} Among 244 randomized clinical trials of

cardiovascular interventions which received a total of \$2 billion in funding from the National Heart, Lung, and Blood Institute from 2000 to 2011, less than two-thirds had published primary results within 30 months of completion.⁶¹ More broadly, from a societal perspective, a large proportion of research funding is wasted when findings are not published, due to either duplication of research or the failure of research to inform future research.⁴⁷

2.2 Industry influence in clinical trial reporting

While many factors likely contribute to nonpublication and publication bias, the potential influence of industry sponsors of clinical trials merits consideration due to cases where sponsor influence has been apparent and due to commercial incentives to selectively report findings.^{23,26,27,62-64} This section of the chapter describes selected cases of sponsor influence, considers commercial incentives of industry sponsors, and describes literature on several themes relating to industry influence which emerged from qualitative interviews conducted for this study. These themes represent factors which may contribute to nonpublication and publication bias, including discontinuation of industry-sponsored trials, ownership and control of data, clinical trial agreements and confidentiality restrictions, and dependency on industry funding.

Cases of industry influence

In several cases, it has come to light that industry sponsors have influenced, or attempted to influence, whether trials with unfavourable findings were published.^{26,62,64} In some cases, companies have taken legal action to prevent publication of negative findings.^{26,64} In other cases, documents from court cases have provided a window into decision-making about reporting related to nonpublication of unfavourable findings.^{26,27}

Steinman et al reviewed internal documents from Parke-Davis to show that the company pursued a “publication strategy” in which they aimed to stimulate off-label prescribing of gabapentin by disseminating findings about off-label uses rather than seeking approval for certain indications.²⁷ Although some within the company felt that unfavourable findings should be published and some negative trials were published, Steinman et al note that “several documents indicate the intention to publish and publicize results only if they reflected favorably on gabapentin.”²⁷ In the case of AstraZeneca’s antipsychotic drug quetiapine, internal documents suggest the intention to selectively publish findings favourable to the company’s drug. “Thus far, we have buried trials 15, 31, 56,” wrote a publications manager. “The larger issue is how do we face the outside world when they begin to criticize us for suppressing data?”²⁶ Similarly, when GlaxoSmithKline agreed to plead guilty and pay fines to resolve fraud allegations in the United States, the allegations regarding the antidepressant paroxetine (Paxil) included both misreporting negative findings from one trial as positive findings and failing to “make available data from two other studies in which Paxil also failed to demonstrate efficacy in treating depression in patients under 18.”²⁴⁻²⁶

Delays in access to clinical trial data may also create a biased body of evidence available to clinicians and policymakers. This can be particularly important in the initial years following the market launch of a drug. In the case of Roche’s anti-influenza drug oseltamivir, the company delayed for years before providing data from published and unpublished clinical trials to independent reviewers that would allow verification of published claims about the drug’s efficacy.⁶⁵ While the drug generated billions of dollars in revenues, many trials remained unpublished.⁶⁶ In fact, *BMJ* has highlighted: “The majority of Roche’s Phase III treatment trials were unpublished a decade after completion.”⁶⁵ Despite public pressure, the company took four

years to provide data in the form of clinical study reports to a team of Cochrane reviewers, who were then able to conduct a systematic review including published and unpublished trials. The review reversed the finding of a previous Cochrane review⁶⁷ and concluded that oseltamivir trials “do not settle the question of whether the complications of influenza (such as pneumonia) are reduced.”⁶⁸

Industry incentives in clinical trial reporting

Industry plays a large role in funding clinical trials,²² and the potential influence of commercial incentives on the integrity of research has been a matter of public debate for some time.⁶⁹ The examples of gabapentin and oseltamivir from the preceding section illustrate the financial rewards for selective publication. The strategy of combining selective publication of gabapentin trials with off-label promotion helped generate revenues of \$2.1 billion from prescribing for off-label uses in the United States in 2002.¹⁷ Similarly, selective publication of oseltamivir trials and delays in providing unpublished data to independent reviewers appears to have been a profitable strategy for oseltamivir, as the company received over \$18 billion in revenue based in part on evidence that independent reviewers later deemed to be uncertain.^{66,68,70} In the context of a drug research system that accords such a large role to industry, the potential influence of commercial incentives of this magnitude in relation to clinical trial reporting or other aspects of research integrity arguably present a major challenge for evidence-based drug policy.

Discontinuation and nonpublication of industry-funded trials

Comparisons of discontinued and completed trials indicate the results of discontinued clinical trials are less likely to be reported.²⁸⁻³³ Although industry-funded clinical trials are typically

found to be no more likely than other trials to be discontinued,^{28-30,71-73} trial investigators have reported in some studies of discontinuation that clinical trials have been discontinued due to a “company/ business decision” or “sponsor decision.”^{33,72-75} Among these studies, this explanation accounted for 6.7% to 16.0% of discontinued trials.^{33,72-75} In one study “administrative reasons” accounted for 15.4% of discontinued trials and included “strategic decisions from companies,”³⁰ while in another study “committee recommendations” accounted for 21.1% of discontinued trials and included “corporate reasons unrelated to safety and efficacy” and “changes in company strategy” among other reasons.²⁹ When trials are discontinued for business or strategic reasons, the underlying motivations may vary. However, these findings may suggest that in some cases industry-sponsored trials are stopped early when either interim results from a trial or results from other trials within a trial program are unfavourable.

Ownership and control of data

Concerns about industry sponsor ownership of clinical trial data or investigator access to data in industry-sponsored trials have existed for at least two decades.^{69,76-79} In 2001, the International Committee of Medical Journal Editors (ICMJE) added a requirement for manuscripts submitted to leading journals that the responsible author declare that he or she had full access to the study data,⁷⁹ and the ICMJE currently advises that “[a]uthors should avoid entering in to agreements with study sponsors . . . that interfere with authors’ access to all of the study’s data.”⁸⁰ These concerns have typically focused on the ability of investigators to conduct independent analysis, and lack of access has been viewed as a threat to investigator independence from commercial influence.^{69,76-79} However, the lack of protections for full access to clinical trial data would

appear to weaken the position of an investigator who wished to assert the right to publish findings against the wishes of a sponsor who was reluctant to publish unfavourable results.

Findings from studies that have examined accepted practices regarding industry sponsor ownership of clinical trial data and investigator access to data in multicentre trials may therefore have implications for reporting of trial results.⁸¹⁻⁸³ A survey of US medical schools asked administrators to estimate the proportion of clinical trial site agreements and coordinating centre agreements that required access to all data for authors of reports on multi-centre trials.⁸³ It found that a median of 1% (interquartile range [IQR], 0-21) of clinical trial site agreements and 50% (IQR, 10-95) of coordinating centre agreements required access to all data. Another survey of US medical schools found that 80% of medical schools would allow a clause that an industry sponsor would own the trial data, and 35% would allow a clause that the sponsor will store the data and release portions to the investigators.⁸¹ A survey of Canadian investigators asked about their experiences conducting clinical trials.⁸² Among investigators who had participated in industry-funded trials over a 5-year period, a majority indicated the funder owned the data in all trials (37%) or some trials (25%). When investigators were asked whether they had access to data from all sites in industry-funded trials, only a minority indicated they had access to data from all sites in all trials (22%) or some trials (23%).

Clinical trial agreements and confidentiality restrictions

Restrictive provisions in clinical trial agreements represent a potential threat to publication of clinical trial results. In the case of Nancy Olivieri, Apotex attempted to prevent disclosure of information to patients and to the scientific community about harms related to deferiprone.⁸⁴ Dr. Olivieri had signed a clinical trial agreement that put restrictions on disclosure of information

from a deferiprone trial to third parties and required her to seek approval from the company prior to submitting findings for publication.⁸⁴ After controversy developed concerning the case of Dr. Olivieri, the University of Toronto and affiliated hospitals developed principles to govern clinical research contracts.⁸⁵ The publication policy developed by the university in 2007 states that agreements cannot preclude disclosure of research results to study subjects and requires that university research must be publishable.⁸⁶

A survey of US medical schools found that almost none (1%) would allow a clause indicating that an industry sponsor may decide that results should not be published.⁸¹ However, another survey of US medical schools found that few clinical trial agreements in multicentre trials require publication of research results, whether agreements are with a site (median 0%; IQR, 0-10) or a coordinating centre (median 5%; IQR, 0-75).⁸³ In a survey of Canadian clinical trial investigators, a majority of respondents who had signed contracts with an industry funder (56%) indicated that all of the contracts they had signed over a 5-year period contained confidentiality clauses, where a confidentiality clause was defined as an agreement not to disclose any or all information about a trial without permission from the funding source.⁸²

Another issue explored in surveys of US medical schools is the right of site investigators to publish within the context of a multicentre trial.^{81,83} One survey found the most site agreements would allow site investigators to analyze and publish site data (median, 100%; IQR, 75-100).⁸³ Similarly, another survey found that few medical schools (15%) would allow a clinical trial agreement to prohibit individual site investigators from publishing manuscripts independently of the group.⁸¹ These findings indicate site investigators in multisite trials may typically have the ability to analyze and publish results based on local site data. However, from the broader perspective, this extends a very limited right to publish to individual sites, as data from a site of a

multicentre trial would not likely provide very reliable findings in most cases due to limited statistical power.

Dependency on industry funding

In the US, industry support for biomedical research increased substantially after the mid-1970s.⁸⁴ The proportion of US medical research funded by industry grew from 46% in 1994 to 58% in 2012.²² The pharmaceutical industry increasingly funded late phase clinical trials rather than preclinical research over the period from 2004 to 2011, while the National Institutes of Health (NIH) continued to allocate the majority of its funding to basic research.²² In 2011, industry and public sources accounted for \$66.6 billion and \$50.5 billion in funding for medical research in the US, respectively.²²

Industry funding of medical research in Canada is also substantial and was estimated at \$1.3 billion in 2011, in comparison to \$1.8 billion from government agencies, higher educational institutes and not-for-profit organizations.²² In the mid-1990s, the federal government implemented a 10% cut over three years to the budget of Canada's major public funder of health research (the Medical Research Council, the predecessor of the Canadian Institutes of Health Research).⁸⁷ In the funding environment of the time, Canadian universities and hospitals increasingly turned to the pharmaceutical industry for funding support.⁸⁴ The Medical Research Council also initiated collaboration with industry to provide funding for medical research during the 1990s,⁸⁷ although some researchers later expressed concern that the model of requiring matching funds oriented research toward "short-term goals of industry partners" and away from awarding grants based on scientific excellence and peer review.⁸⁸

Although public and nonprofit funders are major contributors to medical research, clinical investigators and research institutions such as universities and hospitals have come to depend on industry funders to provide a substantial proportion of funding for medical research, particularly in the area of clinical trials.²² The funding provided by nonindustry funders for investigator-initiated clinical trials may often be inadequate with respect to the budget allocated for conducting a trial,^{89,90} and this may contribute to a dependence of researchers on industry funding.

As the proportion of funding provided by industry for biomedical and clinical research has increased, some have observed that this model of funding may come with trade-offs.^{69,84,91} According to one former medical journal editor, academic medical centres accepted terms from industry sponsors that may compromise their ability to publish and other aspects of research integrity, in part due to competition from contract research organizations who could facilitate research outside of academic settings.⁶⁹ Other authors^{84,91} have suggested that the shift toward increased industry support for medical research may undermine traditional norms of science,⁹² such as disinterested inquiry and the open exchange of ideas.

2.3 Factors contributing to nonpublication and publication bias

This section of the chapter surveys the literature on factors which may contribute to nonpublication and publication bias. The studies described below have approached this subject in various ways. Some systematic reviews have analyzed whether clinical trial design and funding source are associated with nonpublication.¹⁻³ As noted above, studies of clinical trial discontinuation are also relevant to nonpublication, because trials that are stopped prematurely are published less often than completed trials.²⁸⁻³³ Studies of discontinuation have considered the

frequency and determinants of early stopping of trials. Surveys of trial investigators involved in unpublished trials have asked investigators to provide reasons for nonpublication,^{14,35} while other survey studies have asked researchers or journal editors about their views of nonpublication or publication bias.^{93,94} A small number of studies have investigated whether journal editors or reviewers are biased toward positive manuscripts.^{34,95-97} Finally, some articles have considered whether incentives within academic research contribute to nonpublication and publication bias.⁴⁶⁻

48

Clinical trial characteristics, funding source and nonpublication

According to systematic reviews of cohorts of clinical and other biomedical studies, certain study design characteristics are associated with publication.¹⁻³ Two systematic reviews found that clinical trials with a randomized² or both randomized and controlled¹ design are more likely to be published than other clinical studies. One systematic review reported that phase 3 or 4 trials were more likely to be published than phase 1 or 2 trials,¹ while another found that phase 3 trials were more likely to be published than phase 2 trials.³ Multicentre studies are more likely to be published than studies conducted at a single centre.¹⁻³ Although two systematic reviews found that sample size was not associated with publication when all types of studies were considered,^{2,3} one of these reported that a larger sample size increased the probability of publication of randomized or controlled trials.²

Systematic reviews have also analyzed the influence of type of funding on whether clinical or other biomedical studies are published in journal articles.¹⁻³ A systematic review of reports on clinical studies found industry-funded studies were less likely to be published compared to studies with other types of funding (OR, 0.81; 95% CI, 0.67-0.99).¹ Another systematic review

found government-funded studies from trial registries were more likely to be published than industry-funded research (OR, 2.2; 95% CI, 1.7-2.9).³ However, the same review did not find that government funding of studies approved by REBs, compared to industry funding, was associated with trial publication (OR, 1.2; 95% CI, 0.8-1.9). In addition, a systematic review of reports on biomedical abstracts found that industry funding may be associated with an increased probability of publication (RR, 1.18; 95% CI, 1.00-1.40), compared to studies with other sources of funding or no funding.² Although some findings suggest an association between the type of funding and publication, none of these reviews included analysis specific to the association between funding and clinical trials, and it is difficult to interpret the inconsistent findings on this issue.

Discontinuation and nonpublication of clinical trials

Among studies of discontinuation, those that have compared rates of publication in discontinued and completed clinical trials have consistently found that discontinued trials are less likely to be published.²⁸⁻³³ For example, head and neck cancer randomized clinical trials in ClinicalTrials.gov were less likely to be published if the trial had been discontinued (31.6%), compared to completed trials (59.8%).²⁹

Some studies have analyzed rates of discontinuation of clinical trials. A study of all randomized clinical trials approved by 6 REBs in Canada, Germany and Switzerland between 2000 and 2003 found that 24.9% were discontinued.³⁰ Similarly, a study of all clinical drug trials approved by 28 REBs in the Netherlands in 2007 found that 17.8% were terminated early.³² Recent studies of clinical trial discontinuation in registered clinical trials relating to several areas of medicine have reported rates of discontinuation ranging from 7.5% to 30.2%.^{29,31,33,73-75,98-100}

Poor recruitment or lack of patient accrual is most commonly found to be the top reason reported by investigators for discontinuation, given as a reason for discontinuation in 13% to 44% of discontinued trials.^{28-31,33,71-75,98,101,102} Other reasons reported by investigators vary. Some studies^{31,33,73,75} have reported informative termination as a common explanation for discontinuation, which has been defined as “changes in standard of care and safety or efficacy findings.”³³ As noted in section 2.3, trials investigators have also reported that trials are sometimes discontinued by industry sponsors due to a business or strategic decision.^{29,30,33,72-75}

Among studies of discontinuation that have used multivariable models to investigate whether funder or sponsor type was associated with discontinuation, findings have varied.^{28-30,71-73,98} Some studies of randomized clinical trials have found that trials with an industry funder or sponsor were less likely to be discontinued, compared to trials with an investigator sponsor,³⁰ funding from an academic institution,⁷² or public funding.²⁸ However, a study of registered cardiovascular clinical trials found that trials sponsored by industry rather than an academic institution were more likely to be discontinued.⁹⁸ Two other studies found no association between clinical trial discontinuation and funding.^{29,71} Lastly, an analysis of randomized clinical trials studying rare diseases found that industry-funded studies were less likely to be discontinued due to poor accrual.⁷³ It is likely that industry-funded clinical trials have greater resources available to recruit participants,⁷³ which may help explain the finding among some studies that industry-funded studies are less likely to be discontinued.

Reasons given by investigators for nonpublication

A systematic review included studies that surveyed investigators of medical and health-related studies about the reasons for not publishing findings.³⁵ Most unpublished studies had not

been submitted for publication (median, 85%; range, 55% to 100%). Investigators frequently stated that lack of time or low priority was a reason for nonpublication. Investigators also stated research was not published because studies were incomplete or ongoing, studies were not intended for publication, a manuscript was in preparation or under review, fear of rejection by journal, the result was unimportant or negative, they had an author or co-author problem, or they had a sponsor or funder problem.

Findings from another systematic review of studies that surveyed investigators about the reasons for nonpublication were similar.¹⁴ Among studies of clinical trial reporting, common reasons given for nonpublication were lack of time and/or resources, lack of time, and low priority. Other reasons for not publishing findings of clinical trials included trouble with co-authors, results not important enough, incomplete study, negative results, expect journal rejection, and publication not permitted by sponsor.

Studies which have surveyed investigators to ask for reasons for nonpublication provide a useful perspective on factors contributing to nonpublication.^{14,35,103-109} These studies highlight practices leading to publication bias, including not publishing findings that are negative or considered unimportant.^{14,35} Some investigators indicated that sponsors influenced whether findings were published,^{14,35} which represents another source of bias. However, some findings from this type of study are difficult to interpret. Rejection or fear of rejection of journal submissions were not major reasons given for nonpublication, but responses such as “lack of time” or “low priority” may reflect that investigators anticipated that negative or uninteresting results would be difficult to publish, or publish in a high-impact journal.³⁵

While many studies of nonpublication have asked investigators about their reasons for not publishing, a smaller number of studies have asked researchers for their views on nonpublication

and publication bias.^{93,94} A survey of clinical and other researchers found that most researchers (85%) believed that the results of both interventional and observational clinical studies should be published regardless of outcome, and many expressed that nonpublication represents a serious problem in health care.⁹⁴ Similarly, a survey of journal editors and researchers from medicine and other disciplines found that 89% of editors and 90% of researchers felt that publication bias was a problem.⁹³ These studies suggest many researchers value reporting of research results and are aware that publication bias is a problem, although these studies provide little detail on the reasons behind researchers' views on the importance of publishing or addressing nonpublication.

Role of journals

As noted above, many unpublished medical and health-related studies have not been submitted for publication and investigators did not commonly report journal rejection or fear of rejection as reasons for nonpublication, although other reasons given by investigators for nonpublication may also reflect concern about the difficulty of publishing negative results.^{14,35} While drawing attention to the role of investigators in nonpublication and publication bias, these studies do not directly address the role of journals. Studies which have investigated the role of journal editors and reviewers in publication bias are described below.

Some observational studies have analyzed whether journal editor decisions contribute to publication bias.⁹⁵⁻⁹⁷ A study of manuscripts submitted to *JAMA* from February 1996 to August 1999 included prospective studies with an intervention and a comparison group, and found that studies with a significant finding were no more likely to be published than other studies (OR, 1.30; 95% CI, 0.87-1.96).⁹⁷ Similarly, a study of original research submitted to *BMJ*, *Lancet*, and *Annals of Internal Medicine* during January to April 2003 and November 2003 to February 2004,

excluding case reports, found that studies with a significant results were no more likely to be accepted by these journals (OR, 0.83; 95% CI, 0.34-1.96).⁹⁵ Lastly, a study of clinical and basic science studies submitted to *The Journal of Bone and Joint Surgery* during January 2004 to June 2005, excluding those without an abstract or without an evaluation of some kind, found that studies with a favourable result or conclusion for the experimental item were not more likely to be accepted for publication (OR, 0.92; 95% CI, 0.62-1.35).⁹⁶ While these studies controlled for study characteristics and quality, as observational studies they may have been susceptible to bias. For example, as investigators are less likely to submit negative studies for publication,⁹⁵⁻⁹⁷ they may have preferentially submitted negative studies which differed on factors that were difficult to measure, such as studies which were of greater interest or clinical importance.

In contrast to observational findings about the role of journal editor decisions in publication bias, a randomized controlled trial of reviewers' manuscript assessments and recommendations for *The Journal of Bone and Joint Surgery* and *Clinical Orthopaedics and Related Research* suggests that reviewers are influenced by study outcomes.³⁴ Reviewers for these journals received a version of a fabricated manuscript of a clinical trial showing either a positive finding or no-difference finding regarding postoperative use of an antibiotic in addition to preoperative use of the drug. The study found that reviewers were more likely to recommend the manuscript with positive results for publication (97.3% vs 80.0%; $p < 0.001$). In addition, reviewers detected more errors in the manuscript with negative results and rated the methods more favourably in the positive version of the manuscript. The magnitude of publication bias found in systematic reviews of publication bias typically exceeds magnitude of bias found in this study,^{1,3} and it is unclear whether the findings would hold for acceptance decisions made by editors and generalize to other types of journals. However, strengths of the study include its randomized design and its

analyses of error detection and ratings of methodology, which give insight into how publication bias may occur.

Overall, the studies described above provide a mixed picture of the role of journals in publication bias. Journals may contribute to publication bias, but are likely directly responsible for only a small part of this problem. However, journals may also contribute to publication bias indirectly, because investigators may respond to bias they perceive among journal reviewers by focusing their efforts on submission of positive manuscripts. While journals may play a role in publication bias, it is also worth considering other ways in which the research system may influence investigators to preferentially report positive studies. This is a concern which underlies a growing literature on academic incentives, which is discussed in the following section.

Academic incentives in reporting of research findings

Research institutions may use measures such as the number of articles published and the number of citations when assessing researchers in academic hiring, promotion, and tenure.^{48,110} Similarly, research institutions and funders may assess researchers in part based on the journal impact factor of their publications.^{47,48,111} Incentives to publish can be effective in changing researcher behaviour, as illustrated by a study of submissions to the journal *Science* from 30 countries over a 10-year period.¹¹² The study analyzed incentives introduced by some countries to encourage publication in international journals, and found that the introduction of incentives for publishing related to career advancement were correlated with the number of articles published.¹¹² However, while use of publication metrics by research institutions and funders incentivizes publication, it does not necessarily create an incentive for investigators to report results from all of their studies. According to one commentary, biomedical researchers are

rewarded for “claiming novel, significant results”, so they may respond in part by not pursuing publication of negative findings from high quality studies.⁴⁶ In addition, these publication metrics may not reliably measure research quality,⁴⁷ or reflect the contribution of a researcher’s work to society.⁴⁸

Researchers have also provided their views on publication culture.^{93,94,113} A focus group study of biomedical researchers found that perceptions of publication culture were mostly negative.¹¹³ According to the focus group participants, this culture was characterized by hypercompetition for scarce funding and pressure to publish in high-impact journals and to obtain funding.¹¹³ Most participants felt that negative or neutral results were more difficult to publish and that positive results were required to obtain funding.¹¹³ In a survey of journal editors and researchers, many respondents were critical of the culture of science, including pressure to publish in high-impact journals.⁹³ In addition, another survey study concluded that "researchers are aware of being the main culprits of nonpublishing or selective publishing of results from clinical trials", but "they felt strongly that the blame rested not solely with them but with the system that encourages and supports practices that lead to publication bias—from funders and research institutions to journals and trial registries."⁹⁴

2.4 Dissemination of research findings as a duty to clinical trial participants

Many researchers have asserted that investigators have an obligation to clinical trial participants which requires them to publish their findings.^{19,40-43,114-116} Prospective trial participants may reasonably assume or even be told that by participating in a clinical trial they will be contributing to the advancement of knowledge or helping future patients.¹⁹ Since sharing findings with the scientific community through publication is an important component of

ensuring that findings contribute to knowledge and help future patients, some argue that failing to publish findings represents a betrayal of clinical trial participants.^{19,40}

Similarly, some researchers have suggested that nonpublication undermines informed consent or represents a violation of an implicit contract between researchers and participants.^{41-43,115} According to one editorial, “We must consider nonpublication essentially as a breach of contract between the researcher and the participant.”⁴² Some suggest that researchers conducting research with human subjects have implicitly entered a “social contract” with either research participants or society.^{43,117} This emphasizes that the “contract” entered into is not a straightforward exchange based solely on providing a direct benefit to individuals but one that involves a benefit to society through a contribution to knowledge.^{43,117} In addition, selective publication may represent exploitation of research participants, because when negative findings not published, researchers have subjected participants to risk without providing social value.¹¹⁶

As arguments that trial investigators have a duty to trial participants requiring them to publish their findings are often based on the premise that participants enroll in trials in part to benefit others, it is helpful that several studies have examined the motivations of clinical trial participants.³⁶⁻³⁹ A systematic review of studies on motivations for participation in cancer and HIV vaccine trials found that personal benefits were commonly cited as motivators for participation but that participants were also motivated by altruistic factors such as advancing medical research and helping the community.³⁷ Among patients recruited to clinical trials in the gastrointestinal and lymphoma units of a specialist cancer centre, patients most often identified their main reasons for trial participation as a belief that “the trial offered the best treatment possible” or that “the trial results could benefit others.”³⁹ Similarly, other studies have found that clinical trial participants are motivated to participate in part for altruistic reasons.^{36,38} In addition,

a survey of non–critically ill patients in a US emergency department found that most patients (84%) felt it was important or very important to make clinical trial results publicly available.¹¹⁸

The notion that investigators have a responsibility to publish clinical trial findings as a duty to trial participants and patients may be considered in light of basic principles articulated in ethics guidelines.^{119,120} The principle of respect for persons involves respecting the autonomy of research participants, who must be informed of risks and benefits of research as part of the basis of informed consent.^{119,120} As noted above, many trial participants agree to enroll in trials guided in part by the belief that their actions will provide a benefit to society, but this benefit and consequently respect for persons are undermined when trial results are not published. The principle of beneficence (in the *Belmont Report*)¹²⁰ involves maximizing possible benefits and minimizing possible harms of research, and similarly, the principle of concern for welfare (in the *Tri-council policy statement*)¹¹⁹ involves achieving the most favourable balance of risks and potential benefits. These principles are violated when clinical trial results are not published, because nonpublication may reduce or deny research benefits.^{41,42} The principle of justice involves ensuring that a person, or a segment of the population, is not denied benefits or unduly burdened with harms. This principle may be violated when negative trial results are not published, because nonpublication not only diminishes the benefits of research and but also may increase the risk of harm to future trial participants (who may be unnecessarily exposed to risks in redundant research).⁴¹

2.5 Policies to address nonpublication and publication bias

The final section of the literature review describes several areas of policy regarding clinical trial reporting while highlighting directions policy may be developed. Regulatory secrecy

regarding clinical trial data provided a context for selective reporting of clinical trials, whereas moves toward regulatory transparency may help encourage a transition toward full reporting of trial results. This review of policy therefore begins with a brief history of how regulators in the US, Europe and Canada have treated clinical trial data from companies as confidential business information prior to more recent policies to publicly disclose summary results of certain trials and (in Europe and Canada) clinical study reports. This is followed by a description of the emergence of clinical trial registries, mandatory clinical trial reporting policies, and moves toward enforcement of these policies. While these areas of regulatory policy are central, several other areas of policy discussed below may also be important in bringing about full reporting of trials. These include policy to address industry influence in clinical trial reporting, pharmaceutical company policies related to clinical trial transparency, changing academic incentives in clinical trial reporting, nonindustry funder policies, and the role of REBs in clinical trial reporting.

Regulatory secrecy and transparency with respect to clinical trial data

Regulators in the US, Europe and Canada gained greater responsibilities during the 1960s for approval of drugs prior to marketing.^{121,122} Regulators in each of these jurisdictions came to treat information provided by manufacturers as confidential commercial information.^{121,122} In the US, a regulatory culture of treating exchanges with manufacturers as confidential was established at around the time of World War I, and the practice of treating information provided by the manufacturer as confidential continued after the regulatory changes of the early 1960s.¹²² The 1966 Freedom of Information Act (FOIA) changed the confidentiality obligations of federal agencies in the US, but the FDA maintained that drug safety and effectiveness data were exempt

and continued to treat these data as confidential.^{121,123} In Canada, drug regulation was initially characterized by greater transparency.^{124,125} During the period of 1887 to 1920, the Canadian regulator published hundreds of bulletins to inform the public about adulterated drugs and other adulterated products, but after that time Canadian drug regulation shifted from openness toward secrecy.¹²⁴ An initial change was that manufacturers of adulterated products were no longer publicly identified, and when the Canadian regulator started requiring the submission of safety information (in the 1950s) and “substantial evidence” of efficacy (in the 1960s) prior to the marketing of drugs, it treated this information as confidential and proprietary (belonging to the manufacturer).^{124,125}

Following legal challenges from Public Citizen and other consumer groups, the FDA began making available summary documents describing the evidence provided by manufacturers to support drug approvals and FDA review of this evidence.¹²³ Summary documents for drugs approved since 1997 are available online, and documents related to approvals prior to 1997 or for indications subsequent to an initial approval may be requested through a freedom-of-information application.¹²⁶ The review information provided includes high-level summary reviews, statistical reviews, and medical reviews with clinical trial summary results.¹²⁶ The summary documents are valuable in synthesizing evidence of drug effects as they may include results from unpublished trials.¹⁸ Problems reported with access to the FDA information include omission of relevant trials from review documents requested through freedom-of-information applications,¹²⁷ delays in accessing requested documents,¹²¹ and the difficulty of navigating and searching through FDA documents.^{19,128} However, the OpenTrials project has recently created an online repository of FDA documents, which have been processed for easier searching.¹²⁹

Medicines regulators in Europe and Canada also release summary information regarding regulatory decisions.^{122,130} The EMA has published European Public Assessment Reports (EPARs) since 2004, including reports on approved medical products, refused applications and withdrawn applications.¹²² However, a study comparing information submitted by the manufacturers to the Institute for Quality and Efficient in Health Care with information in EPARs for 15 drugs assessed by the institute from January 2011 to February 2013 found that important information for assessing the benefits and harms of drugs was missing from the EPARs reviewed.^{131,132} Health Canada started to make available Summary Basis of Decision (SBD) information in January 2005 following approval of a new drug or device.⁸⁷ The information provided explains the information considered in making a decision to approve a product and describes clinical trials reviewed by the regulator.⁸⁷ However, an analysis of SBDs issued from January 2005 to April 2012 found that they were incomplete and not useful to clinicians in their decision-making.¹³³

Regulators have resisted releasing clinical study reports (CSRs) submitted to them by manufacturers, but in November 2010 the EMA announced a policy of releasing CSRs on request.¹³⁴ CSRs are submitted by companies to regulators when seeking marketing authorization for medicinal products.¹³⁵ They contain more detailed information than trial registries and journal articles about the methods and findings of a clinical trial, so they are important for independent review and providing a deeper understanding of benefits and harms of interventions.¹³⁵ The EMA's policy announcement followed a struggle that started in June 2007, when researchers from the Nordic Cochrane Centre requested access to CSRs and protocols from trials of the anti-obesity medications orlistat and rimonabant.¹³⁶ After the EMA refused this request the researchers appealed to the European Ombudsman, who ruled the EMA had

committed maladministration, determined that the relevant documents contained no commercial confidential information and recommended that the EMA grant the researchers access to the documents.¹³⁷ Ultimately, the EMA complied with the recommendation and adopted a policy of releasing CSRs on request.^{134,136} Although the EMA has encountered legal challenges from some pharmaceutical companies, it has been able to maintain the policy.¹³⁸ In addition, in October 2016 the EMA became the first regulator worldwide to routinely release CSRs,¹³⁸ when it began proactively publishing new CSRs online within 30 days of a regulatory decision.¹³⁵

Since this landmark development in trial transparency in Europe, Health Canada has adopted regulations to publicly disclose information about drugs and devices, including CSRs, and begun publishing this information online.¹³⁹ The proactive release of information about new drugs and devices will be phased in over 4 years for different submission and product types, and similar information is available on request for drugs and devices already on the market.^{139,140} The passage of “Vanessa’s Law” in 2014 provided Canada’s Minister of Health with discretion to release drug safety and effectiveness information,¹²⁴ but Health Canada nonetheless subsequently requested that researchers sign confidentiality agreements prior to receiving information.¹⁴¹ In one of these cases, researcher Peter Doshi, who had requested data on 3 human papillomavirus vaccines and 2 anti-influenza drugs, refused to sign a confidentiality agreement and filed for a judicial review.¹⁴¹ In a milestone ruling in 2018, the court ordered the regulator to release the relevant CSRs and electronic datasets to the researcher.¹⁴¹ In the following year, Health Canada took the additional step of starting to proactively release information about new drugs and devices.¹³⁹ In contrast to both the EMA and Health Canada, the FDA lacks a program to post CSRs.¹³⁹

The disclosure of CSRs submitted to regulators for marketing authorization provides additional transparency, which is complementary to reporting of trial results in registries and journals. Key benefits of disclosure of CSRs include providing data that may be used to verify reports from other sources (such as journals and registries), helping to provide a more complete understanding of efficacy and harms, and serving as a source of data for evidence synthesis.^{135,142} Importantly, disclosure of CSRs by regulators may also serve to provide information about trials not reported in registries or journals.¹⁴³ However, regulators may not be in possession of all CSRs for a medicinal product,¹²¹ so even if the current mechanisms for the release of CSRs are expanded to other jurisdictions, they do not promise to provide full reporting of clinical trial information. If companies were compelled to make clinical data from all trials that have been conducted publicly available, in the form of CSRs or anonymized patient-level data, the benefit for understanding drug benefits and harms would be much greater.^{19,143}

Registries and mandatory reporting

Clinical trial registries represent a key strategy to provide transparency in clinical trial research and to address publication bias. The US registry ClinicalTrials.gov was established under the FDA Modernization Act (1997) and became publicly accessible in 2000. The ICMJE subsequently required registration of clinical trials as a condition of publication in leading medical journals after 2005.¹⁹ The FDA Amendment Act (FDAAA) of 2007 expanded registration requirements, and importantly, required reporting of results in ClinicalTrials.gov from trials within 1 year of completion of data collection on the primary outcome, although phase 1 studies and early feasibility trials of devices are exempt from this requirement.^{44,144} The US Department of Health and Human Services developed a “final rule” regarding the legislation

to clarify and update registration and reporting requirements.¹⁴⁴ The final rule took effect in January 2017, and the first trials affected became due to report findings in early 2018.⁴⁴ In Europe, clinical trials of medicinal products conducted in a European Union country since 2004 must be registered in the European Union Clinical Trials Register (EUCTR), and sponsors are required to report results in the registry within 12 months of trial completion for all trials except most phase 1 trials.⁴⁵ In Canada, the federal government has not established a national clinical trial registry⁸⁷ or introduced mandatory reporting requirements.

Some studies have evaluated whether trial registration is associated with reporting or positive findings.^{53,145-147} A cohort study of all initiated clinical trials approved by a Finnish REB in 2007 found that prospectively registered trials were more likely to be published than unregistered trials (68% vs 39%; adjusted OR, 4.53; 95% CI, 1.12-18.34).¹⁴⁵ However, a large study of all primary reports of randomized controlled trials published in December 2012 in PubMed indexed journals found that registered studies were only marginally less likely to report a positive finding for a primary outcome (risk ratio, 0.87, 95% CI 0.78-0.98).⁵³ Among smaller studies, a study of published reports of cardiovascular randomized trials found that trials reported as registered were less likely to report positive findings,¹⁴⁶ but a study of published reports of randomized controlled trials of new oncology drugs did not find an association between prospective registration and significant findings or favourable conclusions.¹⁴⁷ Trial registration may be associated with increased reporting and reduced publication bias, but the impact of registration alone appears to be modest.

Studies examining compliance with requirements to report within trial registries have found low overall compliance.^{44,45} An evaluation of compliance with the requirement to report within ClinicalTrials.gov covering the period from March 2018 to September 2019 found that 40.9%

(95% CI, 39.4-42.2) of trials reported findings on time, and 63.8% (95% CI, 62.4-65.3) reported findings at any time during the study's follow-up.⁴⁴ Following the final date for compliance with the EUCTR reporting requirements in December 2016, a study covering trials completed on or before December 19, 2016, found that only 49% (95% CI, 48.4-50.7) had reported results in the registry.⁴⁵ The poor rates of compliance with mandatory reporting requirements are consistent with systematic reviews of studies included in trial registries.^{1,3}

Industry sponsors have been more compliant with requirements to report results in these trial registries than other sponsors.^{44,45} Industry sponsors were more likely to report findings within the required timeframe in ClinicalTrials.gov compared to nonindustry, non-US government sponsors (50.3% vs 33.8%; adjusted OR, 3.08; 95% CI, 2.52-3.77).⁴⁴ In Europe, industry sponsors were substantially more likely to report findings in EUCTR compared to nonindustry sponsors (68.1% vs 11.0%; adjusted OR, 23.2; 95% CI, 19.2-28.2).⁴⁵ Reporting requirements were retroactive for EUCTR but not for ClinicalTrials.gov,^{44,45} and this likely helps explain the greater difference in reporting rates between industry-sponsored and other trials in the EU registry, because industry may have had greater capacity to fulfill retroactive reporting rules.

Clinical trial registries and requirements to report results within registries have improved transparency, but some limitations in their design and application have limited their effectiveness. Phase 1 trials are excluded from requirements to report in ClinicalTrials.gov,¹⁴⁴ and most phase 1 trials do not need to be reported in EUCTR.⁴⁵ Reporting deadlines for ClinicalTrials.gov may be extended for up to 2 additional years “if the sponsor certifies that it intends to continue development of the drug, biologic, or device product for initial approval by the FDA.”¹⁴⁴ Poor compliance with reporting obligations may be related to the lack of penalties for not reporting findings in EUCTR⁴⁵ and the lack of enforcement of possible fines for not

reporting findings on time in ClinicalTrials.gov.^{44,148} When the EU Clinical Trials Regulation comes fully into force (anticipated in late 2021), it will become applicable domestic law in member states and require them to introduce “effective, proportionate and dissuasive” penalties for noncompliance with reporting requirements.^{149,150} In April 2021, US-based Acceleron Pharma was sent a notice of compliance by the FDA communicating that it must report findings from a trial it was overdue to report in ClinicalTrials.gov or it could be subject to financial penalties.¹⁵¹ This unprecedented action by the FDA may signal the beginning of greater enforcement of reporting requirements in the US.¹⁵² After issuing the notice of compliance, the FDA stated that it would “encourage voluntary compliance” but “take appropriate actions to help ensure that required information is available on ClinicalTrials.gov as required by law.”¹⁵³

Addressing industry influence on clinical trial reporting

Industry sponsors may be in a position to influence analysis and reporting of clinical trials in part by claiming ownership of clinical trial data and controlling access to data, rather than ensuring that all investigators in multisite trials have access to all of a study’s data.^{81,82} It seems incongruous that regulators in Canada¹³⁹ and Europe⁴⁵ now disclose clinical trial data to non-investigators following regulatory decisions, but investigators who have helped generate a trial’s data may lack access to the same data for the purpose of interpretation and reporting of results. This appears to be an area where regulators could act to protect the right of investigators to access all the data from a trial.

Industry sponsors may have an incentive to engage in selective reporting of clinical trial findings to favour their products. Although industry sponsors have been more compliant with requirements to report results in trial registries, approximately half of industry-sponsored trials in

ClinicalTrials.gov and almost a third of industry-sponsored trials in EUCTR were not reported on time.^{44,45} Monitoring and enforcement of fines may improve compliance.^{44,45} However, financial penalties may not change incentives of reporting for some drugs,¹⁹ because fines might be less than the potential impact on revenues of reporting unfavourable results.

In view of commercial incentives and the bias associated with commercial influence, several authors have called for reforming the research system to rely primarily or wholly on clinical research conducted independently of industry.^{84,154-159} These proposals take various forms. One proposal advocates creating a national institute within the NIH which would be funded at least in part by a percentage of drug company revenues and would contract with independent researchers at academic medical centres to conduct clinical trials.¹⁵⁴ Another proposal suggests a European Institute of Public Health could be established to “have the overall responsibility for developing drugs and bringing them to market, in collaboration with a network of institutions,” and envisions transitioning to a nonprofit research system without patenting of drugs and devices.¹⁵⁶

Pharmaceutical company policies related to clinical trial transparency

An audit of pharmaceutical company policies on transparency included 23 of the top 25 companies by revenue and 19 smaller firms.¹⁶⁰ Among the large companies, 91% had policies expressing a commitment to register all trials, but overall only 71% of all companies had a policy stating they would register all trials. Most of the large companies committed to make all summary results available (96%), and a majority (74%) had policies that committed to reporting results of past trials; however, policies for reporting summary results commonly lacked a

timeline for disclosure. In addition, among large companies, 74% had a policy on sharing clinical study reports on request, and 96% had a policy on sharing individual patient data.

Industry data sharing has provided increasing access to de-identified patient-level data, which has increased transparency.^{161,162} According to an assessment covering January 2013 to May 2017, a data-sharing platform initiated by GlaxoSmithKline had expanded to host data from studies sponsored by 13 pharmaceutical companies and to offer access to 3,374 clinical trials.¹⁶² Although interested third parties must apply for access to the data, data requests are now reviewed by an independent panel managed by the Wellcome Trust.¹⁶²

Although many larger companies have made commitments to sharing individual patient data and to other transparency measures,¹⁶⁰ it remains somewhat unclear to what extent these policies are translating into greater transparency. The audit described above focused only on company policies rather than performance and noted that assessing compliance would actually be difficult due to ambiguities or even internal contradictions often found in these policies.¹⁶⁰ An important concern is that data sharing focused on electronic individual patient data may not be as useful as sharing of case report forms.¹⁶³ For example, case report forms were important to findings relating to harms from paroxetine in the re-analysis of GlaxoSmithKline's Study 329.¹⁶⁴ In addition, the median start date of pharmaceutical transparency policies are "so recent as to exclude the majority of trials on currently used treatments."¹⁶⁰

Changing academic incentives in reporting of research findings

As current academic incentive structures do not effectively incentivize full reporting of research in either journal articles or trial registries, several articles have recommended changes to restructure investigator incentives.^{17,46-48,148,165} These articles typically propose that research

institutions and funders adopt performance metrics that take into account whether researchers have fully reported results of their research.^{17,46-48,148} Similarly, a review of the requirements for reporting results and the state of results reporting in ClinicalTrials.gov suggested investigators receive academic credit for reporting findings in the registry to encourage reporting.¹⁶⁵ While the actions of academic researchers are shaped in part by the incentives inherent in university hiring and promotion decisions, universities are in turn motivated in part by the need to generate institutional revenue.⁴⁷ It is therefore important that some critics of current investigator incentives have recommended changes in use of publication metrics by not only research institutions but also funders.^{17,46,47}

Nonindustry funder policies related to clinical trial reporting

As noted above, one way that nonindustry funders may promote full reporting of clinical trials is through how researchers are assessed when they apply for funding. In late 2020, CIHR publicly stated it would develop policy guidance in 2021 on clinical trial reporting.¹⁶⁶ This will include a requirement that grant applicants must provide information about the reporting status of previous trials when applying for funding,¹⁶⁶ which could encourage results reporting among applicants. The San Francisco Declaration on Research Assessment (DORA) includes a recommendation that funding agencies should “clearly highlight . . . that the scientific content of a paper is much more important than publication metrics or the identity of the journal in which it was published.”¹⁶⁷ While some CIHR grant evaluation criteria incorporate this recommendation,¹⁶⁸ it could be more consistently conveyed to reviewers of applications for clinical trial funding. For example, this approach to evaluating academic productivity is not

described in CIHR's Project Grant peer review manual, which may be used for assessing applicants for funding to conduct clinical trials.¹⁶⁹

The policies of nonindustry funders on registration and reporting of the clinical trials they fund vary widely.¹⁷⁰ A study of top noncommercial funders of health research globally found that 50% required all trials to be registered, 44% required all summary results to be reported, and 22% specified timelines for reporting.¹⁷⁰ The NIH and the UK National Institutes of Health Research (NIHR) require recipients of funding to register trials and to report results within 1 year, and monitor whether reporting has occurred.^{144,170} While CIHR requires registration and reporting results, the agency has not previously specified a timeline for reporting or audited whether findings have been publicly reported.¹⁷⁰ However, CIHR has stated that it will develop policy guidance in 2021 to require results to be reported within "a 12-month timeframe."¹⁶⁶

Role of research ethics boards in clinical trial reporting

Some have suggested REBs should require timely reporting of results, monitor or selectively audit reporting of previously approved trials, and consider withholding approval of future trials if any current trials are unreported after a specified timeframe.^{19,171,172} It may be possible for REBs to sanction investigators by withholding approval of trials due to reporting practices, although it is unclear if ethics boards are the most appropriate body to enforce timely reporting of trials.¹⁷¹ It would likely be feasible for REBs to monitor reporting of trials they have previously approved, such as reporting within trial registries, although they would require appropriate resources to fulfill this function. REBs could periodically audit reporting of trials they have approved and publicly release the audit results. This might promote accountability for clinical trial reporting practices by indicating the proportion of trials reported by sponsors and by highlighting how

frequently investigators affiliated with a given research institution are involved in unreported trials. Another option would be for REBs to take on the role of supporting research institutions to monitor and support clinical trial reporting of investigators affiliated with their institutions. This is illustrated by programs at some US medical schools which have used data from institutional review boards to help monitor clinical trial reporting and improve compliance with regulatory requirements to report clinical trials in ClinicalTrials.gov.^{173,174}

2.6 Summary

Systematic reviews indicate many clinical trials are not published,¹⁻³ and studies of clinical trial reporting in trial registries show that compliance with regulatory reporting requirements is low.^{44,45} Consequences of nonpublication of trials and publication bias include less informed patient care, harm to patients, and inefficient use of research and health care resources.^{17,21,54} Previous research has provided information about aspects of industry influence on clinical trial research, factors contributing to nonpublication and publication bias, and dissemination of trial results as a responsibility to trial participants.

As pharmaceutical companies sponsor a considerable proportion of clinical trial research,²² it is important to understand potential industry influence in clinical trial reporting. While industry-sponsored trials are no more likely to be discontinued than other trials, clinical trials are sometimes discontinued for business reasons rather than for reasons related to ethics or feasibility.^{28-30,33,71-75} Concerns about industry ownership and control of data have tended to focus on the need for independent analysis,^{69,76-79} but control of data may be relevant to the ability of investigators to report findings. Concerns about clinical trial agreements as they relate to reporting have focused on clauses giving the sponsor control over the decision to publish,

which were found to be rare in a survey of US medical schools.^{81,85} However, it is less clear whether clinical trial agreements adequately protect the ability of investigators to report findings. While industry influence on clinical trial research has long been a concern,⁶⁹ the mechanisms through which industry may influence clinical trial reporting have not been clear.

Several factors likely contribute to nonpublication of clinical trials and publication bias. When trials are discontinued, they are less likely to be published.²⁸⁻³³ Journals may play a small direct role of publication bias,^{34,95-97} although any influence of journals may be increased if investigators respond to perceived bias by submitting fewer negative manuscripts. Surveys of trial investigators have highlighted a range of reasons for nonpublication, including lack of time and/or resources, low priority of the study, lack of importance of the results, negative results, and publication not permitted by the sponsor.^{14,35} However, it is somewhat difficult to interpret common reasons given by investigators for nonpublication, such as lack of time or low priority of a study. Some articles have critiqued emphasis on the number of published articles and the use of journal impact factors by research institutions and funders to assess researchers, which may contribute to selective publication.⁴⁶⁻⁴⁸ While previous research provides insights into reasons for nonpublication of clinical trials, it has not provided an in-depth investigation of factors contributing to nonpublication grounded in the experiences of investigators and others involved in clinical trial research.

Many researchers have suggested that investigators have a duty to trial participants to report clinical trial results,^{19,40-43,114-116} and some believe nonpublication of clinical trials may undermine informed consent or represent a violation of an implicit contract between trialists and research participants.^{41-43,115} Participants in clinical trials may reasonably expect a trial will contribute to medical knowledge, but nonpublication arguably diminishes this contribution.¹⁹

However, previous research has not investigated the views of trial participants on the value of clinical trial reporting or asked trial investigators whether they feel they have a duty to trial participants to report their results.

Several types of policy are relevant to addressing nonpublication and publication bias in clinical trial research. Regulatory requirements to report clinical trial findings in trial registries have been established in the US and EU, and compliance may improve if these jurisdictions consistently enforce reporting rules.^{19,44,152,153} It will likely be important to introduce regulatory reporting requirements to improve reporting practices in Canada. Research institutions and funders are in a position to help incentivize full reporting of trials by adopting performance metrics involving consideration of whether investigators have fully disseminated their research.^{17,46-48,148} It is therefore welcome that CIHR has stated it will be requiring investigators to provide the reporting status of previous trials when applying for clinical trial funding.¹⁶⁶ In addition, REBs could play a role in helping ensure clinical trials are reported by auditing reporting practices, or by helping research institutions to monitor reporting and support investigators to fully report their clinical trial findings.¹⁷²⁻¹⁷⁴

Chapter 3: Industry sponsor influence in clinical trial reporting in Canada

3.1 Introduction

Many clinical trials and other biomedical studies are either not published or only published after a long delay.¹⁻³ A recent systematic review, including studies assessing whether clinical studies were published during an average follow-up time of 4.6 years from completion of data collection, found an average of 52.7% of clinical studies were published.¹ Similarly, a previous systematic review, including studies assessing publication during a minimum of 24 months from trial completion, found 60.3% of randomized controlled trials included in trial registries were published.³ As a result of selective publication, the medical literature is both incomplete and characterized by publication bias.¹⁻³

Nonpublication and publication bias in medical research have contributed to poorly informed patient care and harm to patients.⁵⁴ For example, selective publication exaggerated the efficacy of selective serotonin reuptake inhibitors and other antidepressants,¹⁸ preventing physicians from making fully informed treatment decisions for patients with depression. The harms of incomplete trial reporting have been documented related to several types of drug therapy,¹⁷ including the antibody TGN1412,¹⁷ class I anti-arrhythmic drugs,^{19,20} and the type 2 diabetes drug rosiglitazone.⁵⁷ In addition, selective publication may lead to misallocation of health care resources by creating bias in the published medical evidence.¹⁷

In response to this problem, the United States (US) and the European Union (EU) have introduced mandatory registration and reporting requirements applying to many clinical trials.^{44,45,144} For example, US rules require registration of clinical trials and reporting of their results in ClinicalTrials.gov within 1 year of completion of data collection on a trial's primary

outcome, except for certain trials such as phase 1 studies and early feasibility trials of devices.^{44,144} However, studies examining reporting within ClinicalTrials.gov and the European Union Clinical Trials Register (EUCTR) have found low overall compliance with these reporting requirements.^{44,45}

Many factors appear to contribute to nonpublication of clinical trials. Later phase trials^{1,3} and larger trials² are more likely to be published, whereas discontinued trials are less likely to be published.³⁰ A randomized trial of reviewer behaviour suggests that journal reviewers favour studies with positive findings.³⁴ In addition, the emphasis on publication in high-impact-factor journals as a measure of researcher merit in academic hiring and promotion⁴⁸ may incentivize researchers to focus on novel, significant findings rather than on full reporting of research findings.⁴⁶

While multiple factors contribute to selective publication, the potential influence of the pharmaceutical industry on clinical trial reporting has long been a major concern.⁶⁹ In some cases, internal company documents have revealed the intention to suppress unfavourable results.^{26,27,175} The major role of industry in funding clinical research²² provides potential influence over the reporting of findings. However, the mechanisms through which industry sponsors may influence clinical trial reporting and the experiences of clinical trial investigators in reporting findings in industry-sponsored trials are not well understood.

We conducted a qualitative study of clinical trial reporting in Canada involving interviews with trial participants, trial investigators, and others connected to clinical trial research. Our broader study aimed to investigate factors contributing to nonpublication of clinical trials and ethical issues relating to clinical trial reporting. The analysis reported in this chapter aimed to

understand whether and how industry sponsors of clinical trials influence decisions to report trial results.

3.2 Methods

This study used a grounded theory approach to investigate clinical trial reporting in Canada through semistructured, in-depth interviews.^{49,50} We aimed to conduct interviews with clinical trial investigators, clinical research coordinators, research administrators, REB members, and clinical trial participants. The analysis presented in this paper was informed by interviews with all participants but draws most directly on interviews with those involved in the conduct, administration or ethical review of clinical trials.

Consistent with the methodology of grounded theory, our research design involved an iterative process of data collection and analysis, attention to actions and processes, comparative analysis of the accounts of interview participants, and systematic analysis of data to develop conceptual understanding.⁴⁹ As these analytic strategies are helpful in elucidating social processes,^{49,51} this approach was well-suited to analyzing the complex process of clinical trial reporting, which involves trial investigators, research institutions, research ethics boards (REBs), academic journals, regulators, noncommercial funders and industry sponsors.

The research team for this study included members with expertise in clinical trials, medicine, pharmacoepidemiology, pharmaceutical policy and regulation, qualitative methods, and sociology. One member of the research team (GG) has previously conducted qualitative research of industry influence on pharmaceutical research practices, and another (BM) has undertaken qualitative research on industry funding of patient groups and educational outreach to physicians. No prior relationship existed between members of the research team and interview participants.

Reporting of this study followed the Standards for Reporting Qualitative Research (SRQR) guidelines.¹⁷⁶ Strategies to increase reliability of the study included triangulation between different types of participants and reporting detailed context and quotations.⁵²

Sampling and recruitment

We used purposive sampling to include trialists who had conducted trials in varied fields of medicine, trial participants who had taken part in trials of treatments for a range of medical conditions, and others connected to the conduct, administration or ethical review of clinical trials to provide additional perspectives on policy and practice of clinical trial reporting. We aimed to include participants from different provinces to capture variation in experiences related to differences in policy and practice across institutions and provinces in Canada.

We applied inclusion criteria to ensure that interview participants had experience relevant to our investigation of clinical trial reporting. (**Table 1**) The inclusion criteria required that trial investigators and clinical research coordinators have experience in at least 1 clinical drug trial, REB members have at least 1 year of experience in ethics review of clinical trials, and research administrators have knowledge of policy and practice related to dissemination of clinical trial findings or relations with trial sponsors. Clinical trial participants were required to have taken part in a clinical drug trial while at least 18 years of age, and their participation in a trial must have occurred during the 5 years prior to their interview and concluded prior to recruitment to our study.

Recruitment of past trial participants involved newspaper advertising and requesting cooperation from clinical research coordinators and research centres to seek consent for us to contact individuals who had participated in clinical trials at their centres. We identified other

types of prospective participants in ClinicalTrials.gov,¹⁷⁷ the Canadian Clinical Trials Asset Map database,¹⁷⁸ and the websites of research institutions and ethics boards. Identification of trialists to target for recruitment involved reviewing information that was publicly available online to try to ascertain whether trialists had enough experience in clinical drug trials that they would likely have experience with unpublished trials. For example, universities and other research institutions often provided information online regarding a trial investigator's research interests, experience, and publications. Identifying research administrators to contact involved reviewing online information about those involved as administrators in departments of medicine, faculties of medicine, research institutes, and offices responsible for partnerships with industry. Similarly, identifying members of clinical REBs to contact involved reviewing online lists of REB members.

We followed up by email or telephone with past trial participants who expressed interest in participating in an interview or agreed to be contacted. After compiling lists of trial investigators, research administrators and REB members to contact, we invited participation through an email with an accompanying cover letter and follow-up emails. This was complemented with snowball sampling to attract additional interview participants. We offered a \$50 honorarium to trial participants and trial investigators for their participation.

Data collection

Interviews of about 45 to 60 minutes in length were conducted between March 2019 and April 2021. The research primarily involved one-on-one interviews, with the exception of an interview involving both a trial investigator and a clinical research coordinator. Interviews were held in person or by telephone. Data collection also included shorter follow-up interviews with 4

of 34 participants. Interview guides developed for each type of participant provided a basis for semistructured interviews. (**Appendix A**) One of the authors (RM) conducted the interviews and coded the data.

Additional interviews were held until data allowed for identification and in-depth analysis of key themes relating to industry sponsor influence in clinical trial reporting. The Canadian Institutes of Health Research (CIHR) was also contacted in May 2021 to inquire about a policy mentioned by a trial investigator in a research interview for this study, namely, the agency's policy regarding using grant funds provided for a clinical trial beyond the initially planned end date of the grant.¹⁷⁹ CIHR provided a response by email later the same month.

Data analysis

Interviews were audio-recorded and transcribed, and transcripts were coded using ATLAS.ti, version 8.¹⁸⁰ Data analysis involved initial coding, focused coding, and memo-writing to elicit key concepts from the collected data.⁴⁹ Initial coding of data emphasized coding with “words that reflect action” to allow for exploring implicit or explicit social processes.⁴⁹ Following the constant comparative method of grounded theory, a key strategy throughout the coding process involved comparing incidents described by interview participants to other incidents which were similarly coded.^{49,50} Focused coding and memo-writing were used to identify key themes relating to industry sponsor influence in clinical trial reporting.

Patient and public involvement

A patient advocate was consulted during the planning of this research study. All participants in this study who are interested will receive a summary of the study results, including past trial participants who took part in a research interview.

3.3 Results

The study included interviews with 34 participants from the Canadian provinces of Alberta, British Columbia and Ontario, including 17 clinical trial investigators, 1 clinical research coordinator, 3 research administrators, 3 research ethics board members, and 10 clinical trial participants. (**Table 2**) Among those involved in the conduct, administration or ethical review of trials, a majority were based in a university or academic teaching hospital, although a substantial number were based in other settings. As some interview participants had multiple roles in clinical research, their responses in some cases reflected their experience in both conducting trials and serving as a research administrator or ethics board member. Among trial investigators participating in this study, all had conducted both trials with industry funding and trials with other sources of funding, most had served as a principal investigator for a trial, and most had been investigators in both single-site and multisite trials. Trialists represented a range of medical disciplines, including cardiovascular medicine, endocrinology, hepatology, infectious diseases, oncology, psychiatry, and rheumatology.

We identified several key themes in the study data relating to industry influence on clinical trial reporting: (1) sponsor influence on decision making about whether to publish, (2) weaker incentives to publish trials with negative findings or evidence of harm, (3) stopping trials early and not reporting stopped trials, (4) ownership and control of data, (5) clinical trial agreements and confidentiality restrictions, (6) nonpublication of internal company trials, and (7) dependency on funding from industry-sponsored trials. We elaborate on each of these themes below, including selected quotations from trialists (T1-T17) and research administrators (A1-A3). This is followed by a brief section summarizing and interrelating these themes.

Sponsor influence on decision making about whether to publish

An important theme was that in some cases sponsors play a role in decision making on whether results from industry-sponsored trials are published. In the view of one investigator, the sponsor could exert a high degree of control over reporting findings: “Ultimately . . . the final analysis, publications, etc—all that decision making happens with the sponsor.” (T7) Asked to clarify whether he meant that the decision to publish, or the control of publishing, was in the hands of the company, he replied: “Almost entirely—yes. If it's a company-sponsored trial, then it's almost entirely in their hands.”

Several investigators described cases in which they believed the sponsor had influenced the decision to not publish findings. An oncologist described what he considered to be a “classic example” of industry influence on reporting. Following a phase 1 trial, the company decided not to develop the drug due to its toxicity profile. He had accrued sufficient patients to the trial that he would be coauthor of a publication, but he did not believe the decision to publish was under his control. Asked about when the trial had been completed, he replied: “Probably well over two years [ago]—and I've actually bugged the sponsor to say, are you guys going to publish this?” (T3) A common sentiment in these cases was that site investigators lacked control over reporting of industry-sponsored trials. For example, a cardiovascular researcher who had been a site investigator in unpublished phase 2 and 3 industry-sponsored trials said the decision on whether to publish would be made at a high level in the study organization, and added: “I think that in the case of investigational drugs there is a lot of industry influence.” (T8) However, another trial investigator who had been an investigator in unpublished industry-sponsored trials emphasized that in his experience the presumption in pivotal industry-sponsored trials was that the results would be published.

Weaker incentives to publish trials with negative findings or evidence of harm

A core theme was that industry sponsors have a weaker incentive to publish certain studies, including trials with negative findings, trials showing harms or safety concerns, and trials for drugs which the sponsor decided not to develop further. An oncologist who had been a site investigator in two unpublished phase 3, industry-sponsored trials with negative results explained that “negative trials tend not to be published.” (T12) Other investigators made comments like the following one, which highlighted the incentives of sponsors: “I would say with the companies, there's so much financial incentive for them to report positive results and not to report negative results.” (T15) A few investigators described trials which showed harms or safety concerns and were not published, including a trial that was completed and trials that were stopped early. In some cases the decision not to publish findings followed from a decision not to develop the drug. For example, an investigator in an unpublished cardiovascular drug trial believed the drug worked, but explained: “I guess they determined it was not a business case for further developing and [for] the investment that it required to bring it to market.” (T8)

Several investigators noted that positive findings from industry-sponsored trials also tend to be reported more quickly than negative findings. One investigator described how commercial incentives enter into the timeline of reporting: “Well, if the study . . . meets its endpoint, there is a huge financial incentive to publish this as quickly as possible . . . if the results are positive, you might see a publication come out on the same day as it's presented somewhere—as opposed to it gets presented at a meeting and at some point later somebody takes the time to write up the paper.” (T3)

Some investigators reflected on the incentive of sponsors to report findings whether they are positive or negative. One trialist suggested large trials with clear importance to clinical practice

are likely to be published regardless of outcome. When asked about factors that contributed to a negative vaccine trial being published, another trialist suggested that in part the company may have wanted to create goodwill with investigators.

Stopping trials early and not reporting stopped trials

Some trialists had been investigators in trials that had been stopped early and not published. One investigator involved in cardiovascular research described a phase 3 trial that had been stopped by the data and safety monitoring board of the trial, which he was not aware of having been published. In his experience this was not unique: “And we've had a lot of trials, actually—that for some safety reason that the trial gets halted, and then the result—I mean, everybody knows, who was involved, that the trial was halted but it actually never results in a publication necessarily.” (T8)

Investigators also described their experiences in unpublished trials which had been stopped due a business decision of the sponsor to halt development of the drug, rather than by a data and safety monitoring board, although in one case a drug was later marketed by another company. It is also possible that a small biotech firm sponsoring a trial may not only stop a trial but close down as a company without pursuing publication of trial results. As one oncologist described, if the company holds the data and has not shared the data with investigators, this may make it impossible to publish the findings: “I think these small biotechs—because as soon as their drug dies, if they have their negative study, their company dies . . . and then you're kind of left with nothing.” (T1) He added that when a company decides to stop development of a drug, this may lead to stopping not just one trial but multiple ongoing trials within a trial program: “Let's say there's 20 trials going—from one drug across multiple tumour sites—and then if a few of them

start to fail, they may just shut down the whole program.” Publishing results from discontinued trials, some trialists noted, may also be of less interest to investigators.

Ownership and control of data

In industry-sponsored trials, the sponsor typically owns the key data from the trial and may control access to data by investigators. As noted above, control of data can be important in the context of trials sponsored by small biotech firms. If the company is reliant on a single drug, it is possible the company may close its operations without proceeding to publish or sharing data with investigators to enable reporting of trial findings. More generally, some trialists considered control of data to be an important factor differentiating investigator-initiated or cooperative group trials from industry-sponsored trials, and linked control of data to the ability to publish. For example, an oncologist highlighted that a key difference between industry-sponsored trials and cooperative group trials is that “the cooperative group has complete control over the data.” (T3) While he had been an investigator in unpublished industry-sponsored trials, he suggested that “most of the time you would see [cooperative group] studies published, because we control the data, we control the output, and . . . we want to publish even if the study results are not what we might have expected them to be.” Similarly, a psychiatrist who had been an investigator in trials sponsored by pharmaceutical companies said he preferred to focus on investigator-initiated trials because in company-sponsored trials “you don’t own the data.” (T13) He noted a company has a disincentive to publish negative findings, but a site investigator in a multicentre trial would not have a right to access all of the data from a trial to be able to publish the results. In contrast, he felt that having control over data in an investigator-initiated trial provided freedom to publish:

“You are way better if you can get your own grant, doing your own trial, where you own the data—you can publish what you want.”

Alternatives to the sponsor controlling the study data, one research administrator noted, are models where an academic research organization would either “run the whole trial and have total access to the data analysis” (now less common) or share access to the study database held by the sponsor (a mixed model). (A1) The latter approach, one investigator felt, not only allows for more independent validation of findings but also could help protect against interference with reporting: “Having shared access to the data is another way to protect against industry trying to—or one group trying to—not get the information out there.” (T11) It is unclear to what extent this approach helps ensure reporting of findings, however, and the administrator above felt that the main value of shared access to the study database was to allow for additional analysis and substudies.

Clinical trial agreements and confidentiality restrictions

Several study participants spoke about how clinical trial agreements (CTAs) or confidentiality agreements between researchers and trial sponsors, or contract research organizations, relate to dissemination of research findings. Policies or practices at a research institution may prohibit investigators from entering into contracts that would give up their right to publish, but this might only protect the right to publish results from the local site in a multicentre trial. A university-affiliated investigator described how this would be put into practice in a CTA at his institution:

It basically said that if X amount of time [has] gone by and the company and/or the lead investigators hadn't published that information, then I as an investigator, at least in the contract, had a legal right to publish my

findings. And that was trying to kind of twist the arm and give some time frames to make sure that this information doesn't just get swept under the carpet or buried, particularly if it's a negative result or it's potentially harmful to the stockholders or the company that supported that. The challenge with that is it's not really enough, because if you're doing—as I often do—large multicentre trials, even if I enroll a hundred patients in the study, I can publish my results but I can argue that might not even be ethical because I might have a skewed distribution. I don't have adequate [statistical] power. (T11)

An administrator from another university described similar practices at his institution. In addition, a couple of site investigators mentioned that confidentiality restrictions could prevent investigators from speaking about or reporting findings from an industry-sponsored trial that has not been published. For example, one investigator noted:

Sometimes with these trials you're also signing confidentiality agreements . . . and that prevents you, as an investigator, banging out an article kind of in violation of your confidentiality agreement. I know that's happened, where there was some investigator who felt that a particular drug or a device . . . was harmful, and that information is being suppressed by the trial sponsor, so they write a paper that ends up in lawsuits and all kinds of things. (T8)

Although study participants indicated that a CTA would not give the sponsor the explicit right to decide whether to publish, CTAs may only weakly protect the ability of site investigators to publish and confidentiality restrictions may impose additional constraints.

Nonpublication of internal company trials

An investigator who serves on an REB indicated that many early phase, internal company trials are not published. Some of these clinical trials are for drugs the company has decided not to develop further:

So quite often when a company is developing a molecule—out of probably hundreds or thousands of compounds, they'll get a handful of them that might have some promise. And then they take those into phase 1 and phase 2 And then either because of lack of efficacy or toxicity, or some problem, they elect to not further develop that compound, and then those studies are usually never published. (T8)

Other internal trials are for drugs the company will continue to investigate in larger trials. When reviewing ethics applications for industry-sponsored trials, this investigator often reads about smaller in-house phase 1 and 2 trials the company has conducted previously, which are described in the scientific appendix of a trial protocol or in an investigator's brochure. He believed these internal company trials for drugs still in development are also typically not published.

Dependency on funding from industry-sponsored trials

The accounts of interview participants reflect that researchers and research centres often depend on industry funding for clinical trial research. Funding from public and nonprofit sources tends to be inadequate to cover all the costs involved in conducting a trial. Industry funding provides opportunities for participating in industry-sponsored trial research and may be used to subsidize other trials. While industry funding provides a range of benefits, dependence on industry funding may make it difficult for researchers or research institutions to negotiate terms which enable full reporting of clinical trials.

Several interview participants contrasted the level of funding provided to a site in industry-funded trials with funding provided by public granting agencies or other nonprofit sources. One oncologist characterized the budgets in industry-sponsored trials as “commensurate with the work”, whereas he said that budgets in cooperative group trials are “not high enough to actually conduct the study in a cost-neutral way, so you're usually running a loss in those studies.” (T3)

Similarly, other trial investigators and a research administrator indicated that funding from nonindustry sources tends to be inadequate for conducting a trial. Comparing funding from CIHR to funding from industry for his investigator-initiated trials, one investigator said he also considered funding from industry to be “safer” in that he would not be at risk of losing funding due to delays in conducting the trial, whereas he might be faced with returning funds to CIHR if delays continued for an extended period. The investigator described a CIHR policy which states grant recipients are entitled to an automatic extension to make use of grant funds for 1 fiscal year after the end of a grant (without additional funding), and they may apply for an additional extension of 1 calendar year beyond that under circumstances such as uncontrollable delays.¹⁷⁹ When contacted about this policy, a CIHR representative stated that grant recipients may request further extensions following the automatic 1-year extension and additional 1-year extension, although this is not explicit in the policy.

Investigators from various areas of medicine stated that they used funding from industry-sponsored trials to subsidize trials that did not have industry funding. A few emphasized that funding from industry-sponsored trials ensured that their research centres were able to operate without a deficit. For example, one oncologist described the need for industry funding as follows:

I'm very involved in pharma-sponsored trials, so we run many of those, because as you can imagine, the cooperative groups do not fund [adequately]. And so this is actually a mini-business—in the same sense that you have to hire individuals to run your clinical trials appropriately and in a safe, ethical manner. So that obviously costs money. . . . So these cooperator groups—we don't have a lot of support. It also allows us to run independent or investigator-initiated trials as well. So if you run a whole large clinical trials unit, it tends

to fund. It's kind of a give and take. Your industry-sponsored clinical trials—which are usually global, multicentre, large trials—they remunerate much better per patient compared to the cooperative trials. (T12)

Making use of funding from industry-sponsored trials to fund trials without industry funding appears to represent a common strategy trialists and research centres use to meet funding challenges and carry out their research programs.

Comments from investigators suggest that while industry funding benefits researchers and research centres, depending on funding from industry-sponsored trials may involve trade-offs. First, individual investigators may or may not be able to set the terms of their participation to help ensure that trial results are reported. One investigator imagined the situation of an early career investigator aiming to do independent research. He reflected that “if they can bring in some industry funding while they're working on another project to help support those other projects, that's a model that all of us use to try to do the non-industry-funded [trials].” (T11) He imagined what he would want to be in place as a new investigator taking part as a site investigator in an industry-sponsored trial—such as involvement of an independent academic research organization and language in the trial protocol about the responsibility and approximate time frame for disseminating findings—but acknowledged that new investigators may not be in a position to “pick and choose” which trials to be involved in. Second, research institutions may face difficulties in negotiating terms with industry sponsors that ensure full reporting of trials. When asked whether the university or its research ethics board could take measures to help ensure trials are reported, an investigator at a university-affiliated research centre responded:

I guess if the university wanted to take a hard stand on it, they could, but If it's a big multinational company, then they'll just go somewhere else. And this is where it gets a little bit grey, because to some

extent these contracts do bring in money, they do generate revenue for both investigators and for the university. . . . So there is some revenue coming into the university, and . . . if that revenue is supporting research infrastructure more broadly, then . . . there's always kind of potential unintended consequences if you take a completely hard line. (T7)

The above comment highlights that universities may hesitate to adopt policies to help ensure industry-sponsored trials conducted at university-affiliated sites are reported, due to dependency on industry funding.

Synthesis: industry sponsor influence on clinical trial reporting

A core theme emerging from investigator interviews is that industry sponsors have a weaker incentive to publish trials with negative findings, trials showing harms or safety concerns, and trials for drugs which the sponsor has decided not to develop further. Although unfavourable results from industry-sponsored trials are often reported, the commercial incentives of sponsors represent an important underlying factor contributing to nonpublication and publication bias in industry-sponsored trials.

The position of a company as a sponsor provides influence over the reporting of a clinical trial in various ways. First, sponsors may decide to stop a trial due to a business decision to halt development of a drug, and they may not proceed with reporting the findings from trials stopped for this or other reasons. When a trial is stopped early, publishing the findings may also be less attractive to investigators. Second, it is typically accepted that a sponsoring company will own the key data from a trial, and a company may also centrally house and control access to data from a multicentre trial. Sponsor control of data may hinder the ability of an investigator to report findings in cases where a company does not wish to publish (or in cases where a small

biotech firm closes down when its product fails). Third, clinical trial agreements for multicentre trials may provide only weak protection of the right to publish. Although clinical trial agreements do not generally specify that a sponsor can decide on whether findings are published, it is common for these agreements to only protect the right of site investigators to publish site data rather than all data from a multicentre trial. In addition, internal company trials of investigational drugs may not be published.

Importantly, the structure of the research system in Canada and internationally provides a context in which industry influence on trial reporting may occur. Public and nonprofit funders provide funding that may be inadequate for properly conducting a trial, and governments have left the responsibility for funding a large portion of clinical trial research to industry. While many researchers value and rely on industry funding of clinical trials, dependence on funding from industry sponsors may make it more difficult both for individual researchers and for research institutions to negotiate terms of research to ensure full reporting of research findings.

3.4 Discussion

While selective publication may occur for a variety of reasons, accounts of trial investigators indicate that in some cases industry sponsors influence decisions on whether to report trial findings. Companies have a weaker incentive to publish trials with unfavourable findings and trials for products they have decided not to develop further. The position of a company as a sponsor allows the company to influence reporting in various ways, including stopping trials early and not reporting results of stopped trials, owning and controlling access to data, and negotiating clinical trial agreements in multicentre trials that do not fully protect the ability of investigators to publish. Internal company trials represent an additional source of unpublished

trials. More broadly, the research system creates a dependency on funding from industry sponsors that may weaken the ability of researchers and research institutions to negotiate terms with industry sponsors that would more fully protect publication rights.

Comparison with other studies

Our analysis highlights mechanisms of industry influence on clinical trial reporting, including stopping trials early, not reporting results of stopped trials, and industry ownership and control of data. Aspects of these mechanisms have been explored in previous studies. Studies of trial discontinuation have found that discontinued trials are less likely to be published²⁸⁻³³ and that clinical trials are sometimes discontinued due to a “company/ business decision” or “sponsor decision”^{33,72-75} or due to “strategic” company decisions or “corporate reasons unrelated to safety and efficacy.”^{29,30} In a survey of Canadian trial investigators, a majority of trialists who had participated in industry-funded trials over a 5-year period reported that funders owned the data in all or some trials, and only a minority reported they had access to all data in all or some trials.⁸²

Previous studies have explored how clinical trial agreements either protect or restrict the ability of investigators to report trial results.⁸¹⁻⁸³ Surveys of US medical schools regarding clinical trial agreements indicate that individual sites in a multisite trial may often have the ability to publish local site data.^{81,83} Similarly, an academic-affiliated investigator in our study described a policy at his university to protect the contractual right of investigators to publish data from a local site, but he highlighted that the ability to publish data from one site within a multicentre trial may not be meaningful. Among Canadian trial investigators who had signed contracts with an industry funder, a majority surveyed indicated that the contracts included confidentiality clauses, defined as an agreement not to disclose any or all information about a

trial without permission from the funding source, in all of their industry-funded trials over a 5-year period.⁸²

Previous research has highlighted that academic trials with a nonindustry funding source are often underfunded,^{89,90} which our findings suggest may contribute to a dependence on funding from industry sponsors to deliver clinical research programs. Arguably, a dependence on industry funding is also reflected in the substantial proportion of medical research funding that is provided by industry in Canada, the US and globally.²²

Although phase 3 trials are used for drug approvals and are highly important for providing a more complete understanding of the safety and efficacy of drugs, clinical trials for drugs earlier in their development cycle and drugs a sponsor has decided not to develop further may provide relevant information for future trials and even clinical practice.¹⁹ In 2006, six healthy volunteers in a phase 1 trial of the monoclonal antibody TGN1412 developed cytokine release syndrome with multi-organ failure.⁵⁹ However, an unpublished phase 1 trial conducted more than a decade earlier found that a similar antibody had effects which paralleled those of TGN1412.^{17,59} If the earlier trial had been published, this might have helped avoid the outcome of six individuals experiencing serious adverse events in the trial of TGN1412.^{17,19,59} In 1980, a small trial of the anti-arrhythmic drug lorainide in patients with suspected acute myocardial infarction found an increased risk of death in the treatment group compared to placebo.¹⁸¹ Commercial development of the drug was discontinued.¹⁸¹ If published earlier rather than after a delay of more than a decade, the trial findings might have discouraged the routine prescribing of other anti-arrhythmic drugs to people with heart attacks, which is estimated to have led to over 100,000 premature deaths.^{20,181}

Studies of compliance with requirements to report results in trial registries illustrate that, although industry sponsors have been more compliant than nonindustry sponsors, nonreporting of industry-sponsored trials continues to be a major problem.^{44,45} A study of compliance with the requirement to report results in EUCTR within 12 months of trial completion, covering trials completed on or before December 19, 2016, found that close to a third of applicable industry-sponsored trials registered since 2004 had not reported results.⁴⁵ Similarly, a study of compliance with the requirement to report results in ClinicalTrials.gov within 1 year of data collection on the primary outcome, covering the period from March 2018 to September 2019, found that about half of applicable industry-sponsored trials had not reported results on time and about a third had not reported results at any time.⁴⁴

Policy implications

While the EU and US have adopted requirements to report the results of many clinical trials within trial registries, the EU has lacked penalties for noncompliance and the US has until recently not enforced potential penalties.^{44,45,182} When the EU Clinical Trials Regulation comes fully into force, the regulation will require member states to legislate penalties for noncompliance.^{149,150} In April 2021, the FDA issued an unprecedented warning to Acceleron Pharma regarding potential civil monetary penalties which could apply if the company did not report overdue results from a clinical trial, and the agency publicly stated its intention to take action to ensure sponsors comply with reporting requirements.¹⁵¹⁻¹⁵³ If consistently enforced, mandatory requirements to report clinical trial results could help address the incentive of industry sponsors to selectively report clinical trials.^{44,45,148} However, most phase 1 trials of medicinal products are exempt from EU reporting requirements,^{44,45} and phase 1 trials of drugs

and biologics are exempt from requirements to report in ClinicalTrials.gov.¹⁴⁴ In addition, Canada has not adopted similar regulatory requirements for reporting of clinical trial results. It is important for reporting rules to cover all clinical trials of drugs and biologics and for Canada to adopt regulatory measures to make reporting of clinical trial results mandatory.

Our study highlights that clinical trials stopped early for commercial reasons are a source of unreported trials. While trials may be discontinued for legitimate reasons related to efficacy, safety or feasibility, stopping a trial early for commercial reasons arguably undermines the social benefit of a trial on which informed consent and ethical approval are based.¹⁸³⁻¹⁸⁵ Given that stopping trials early for commercial reasons diminishes the ethical basis for conducting a trial and represents a source of unreported trials, this issue merits further consideration regarding whether regulatory actions should be taken to limit this practice.

When an industry sponsor does not proceed with publishing findings of a multicentre clinical trial, site investigators may lack the ability to report findings from the full trial due to a lack of access to data from the whole trial and a lack of protection of the right to publish in clinical trial agreements. While this is problematic for individual site investigators, it also poses a particular problem for universities because it means university-affiliated researchers are engaged in research with human subjects they may lack the right to publish in a meaningful way. Conducting clinical research that cannot be reported breaches scientific norms of communication of findings and disinterested pursuit of knowledge and may violate research ethics by not fulfilling participant expectations that research will contribute to knowledge.^{41,42,92} Consequently, universities and other research institutions have an obligation to enact policies to better protect the ability of trial investigators to access all data from a trial and the rights of site investigators to report findings based on all data from a trial when the sponsor and trial leaders

do not proceed with timely reporting. While research institutions have a responsibility to act, regulatory action may be helpful in this area as regulators like Health Canada are better positioned than research institutions to bring about wider reforms.

The research system is characterized by a dependency on industry to fund a substantial proportion of clinical research, and it would require much greater public investment to change this. Providing greater support to clinical trial research conducted independently of industry would increase the amount of research that is not subject to commercial incentives to selectively report results. A strategy to lessen the dependence of the clinical research system on funding from industry sponsors would need to involve a higher level of funding per trial and an overall increase in public funding for clinical trial research. Our study also highlights the importance of stability of funding. For example, CIHR grant recipients may require greater flexibility to continue using grant funds following delays experienced in completing a trial, or at least greater clarity regarding the ability to apply for extensions to use funds over a longer period.

Strengths and weaknesses of the study

Strengths of the study include the use of in-depth interviews, which allowed for a detailed exploration of experiences and views of clinical trial reporting, and the involvement of participants with a wide range of experience in the conduct, administration or ethical review of clinical trials. The study also has limitations which merit consideration. The study did not include other types of participants who might provide insights into clinical trial reporting, such as representatives of industry sponsors, medical journals or regulators. We relied on interview participant accounts, which may be limited by participants' perceptions or ability to accurately recall events. While participants described a broad range of experiences and views, we cannot

disregard the possibility that those who chose to participate might differ in important ways from those who did not.

Future research

Our study highlighted several ways that industry sponsors may influence clinical trial reporting in Canada. Among other ways sponsor actions may influence reporting, industry sponsor decisions to stop a trial due to halting development of a drug were associated with nonpublication. In some cases, a small biotech firm may not only stop a trial but also close as a company without proceeding to publish trial results or sharing data with investigators. It may be valuable to assess the frequency of small biotech firms ceasing operations when faced with negative trial findings and leaving investigators without resources to complete ongoing trials or data to report trial results. More broadly, as our study focused on participants in Canada, future research could investigate the generalizability of our findings to other jurisdictions.

Conclusion

Interviews with trial investigators and others connected to clinical trial research in Canada indicate that in some cases industry sponsors influence whether findings from clinical trials are reported. Policies aiming to bring about full reporting of trials could benefit from considering the commercial incentives of companies and the ways in which industry sponsors may influence clinical trial reporting, including stopping trials early and not reporting results of stopped trials, industry ownership and control of data, terms of clinical trial agreements that do not fully protect the ability of investigators to publish, and dependency on funding from industry sponsors. Regulators and research institutions have an obligation to ensure site investigators are able to

report trial findings based on all data from multisite trials, when sponsors and trial leaders do not proceed with timely reporting.

Chapter 4: Factors relating to nonpublication and publication bias in clinical trials in Canada

4.1 Introduction

Clinical trials are essential for informing drug development and clinical practice, but many trials are not published and positive trials are more likely to be published than negative trials.¹⁻³ A systematic review estimated the proportion of studies included in trial registries that were published as journal articles, based on studies of nonpublication assessing publication status after a minimum of 24 months from study completion.³ It found that only 54.2% of all registered studies and 60.3% of randomized controlled trials were published. Nonpublication and publication bias undermine our understanding of the efficacy and safety of treatments and lead to avoidable waste of research and health care resources.^{17,21,54}

The United States (US) and European Union (EU) require results of many clinical trials to be reported within trial registries, and some noncommercial funders of health research similarly require grant recipients to report clinical trials results.^{44,45,170} However, compliance with US and EU regulatory reporting requirements has been low,^{44,45} and a study of top noncommercial funders globally by expenditure found that only a minority required all summary results to be reported and even fewer specified a timeline for reporting.¹⁷⁰

Canada has not introduced regulatory requirements to report clinical trial results, although researchers conducting trials funded by the Canadian Institutes of Health Research (CIHR) are expected to comply with reporting requirements in the *Tri-council policy statement*. This policy requires researchers to report results from CIHR-funded clinical trials “in a timely manner” but not according to a specific timeline.¹¹⁹ However, CIHR has committed to introducing policy

guidance on new requirements for clinical trial reporting during 2021, including mandatory reporting of results within a “12-month timeframe.”^{119,166}

Multiple factors likely contribute to nonpublication and publication bias in clinical trial research. Commercial incentives may contribute to selective reporting of industry-sponsored trials.²³ Systematic reviews have examined factors contributing to nonpublication of biomedical and health-related studies, based on reasons provided by investigators.^{14,35} However, the ambiguity of reasons commonly given for nonpublication, such as a lack of time or the low priority of a study, make these studies difficult to interpret.³⁵

While researchers have clearly documented the problem of selective reporting of clinical trials for over three decades,^{1-3,6,13,15,54} the range and interrelation of factors which contribute to nonpublication and publication bias are less well understood. We conducted a qualitative interview study to investigate factors related to clinical trial reporting in Canada and ethical issues in clinical trial reporting. The analysis reported in this chapter aimed to understand factors contributing to nonpublication and publication bias in clinical trials in Canada.

4.2 Methods

Our study used a qualitative research design involving semistructured, in-depth interviews with clinical trial investigators, a clinical research coordinator, research administrators, research ethics board (REB) members, and clinical trial participants. Our methods for data collection and analysis were informed by grounded theory.^{49,50} We chose this methodology because grounded theory is well-suited for researching social processes such as the process of clinical trial reporting.^{49,51} The backgrounds of members of the research team included clinical trials, medicine, pharmacoepidemiology, pharmaceutical policy and regulation, qualitative methods,

and sociology. We aimed to improve reliability of the study through triangulation of data from different types of participants and providing the reader with descriptions of interview participant responses and accompanying quotations.⁵²

Sampling and recruitment

This study used purposive sampling to create a diverse sample of interview participants. We aimed to include clinical trial investigators from a range of fields, past trial participants from trials of treatments for a variety of medical conditions, and others involved in the conduct, administration or ethical review of clinical trials. We also invited participation from individuals in different provinces in Canada to include a broader range of perspectives. Inclusion criteria for each type of study participant and the rationale for each of these criteria are shown in **Table 1**.

Strategies to recruit past trial participants included newspaper advertising and asking clinical research coordinators and research centres to assist by seeking consent for us to contact past trial participants from their centres. We followed up by email or telephone with anyone who expressed interest or gave consent to be contacted. Several sources were used to identify other potential participants, including ClinicalTrials.gov,¹⁷⁷ the Canadian Clinical Trials Asset Map database,¹⁷⁸ and websites of research institutions and ethics boards. We invited participation by email and recruited additional participants through snowball sampling. Trial participants and trial investigators were offered a \$50 honorarium for participation.

Data collection

Interview data were collected between March 2019 and April 2021. Semistructured, individual interviews were conducted either in person or by telephone based on interview guides developed for each type of participant (see **Appendix A**). One interview involved both a trial

investigator and clinical research coordinator. Interviews lasted approximately 45 to 60 minutes. Shorter follow-up interviews were conducted with 4 of 34 participants in our study. Additional interviews were conducted until data allowed for a thorough analysis of factors relating to nonpublication and publication bias. All interviews were audio-recorded and transcribed. One member of the research team (RM) conducted the interviews and coded the interview data.

In May and June 2021, RM corresponded by email with CIHR regarding the requirements for CIHR-funded researchers to report clinical trial results and the agency's guidelines for assessment of researchers applying for grants to conduct clinical trials. (Questions sent to CIHR and the agency's replies are included in **Appendix B.**)

Data analysis

Analysis of interview transcripts involved a process of initial coding and focused coding, using ATLAS.ti qualitative software, version 8.^{49,180} Initial coding involved developing provisional codes to characterize processes relating to clinical trial reporting and the meanings attached to them by interview participants. At the stage of focused coding, transcripts were re-analyzed to identify, retain and refine the most important codes. Coding and memo-writing informed the identification of key themes relating to factors that influence clinical trial reporting.

Patient and public involvement

Planning the research study included consulting a patient advocate. Study findings will be shared with all participants who expressed interest in receiving a summary of results, including past trial participants.

4.3 Results

Interviews were conducted with 34 participants from the Canadian provinces of Alberta, British Columbia and Ontario. This included 17 clinical trial investigators, 1 clinical research coordinator, 3 research administrators, 3 REB members, and 10 clinical trial participants. (**Table 2**). Some interview participants were able to speak about their experiences as both trial investigators and research administrators or REB members. Specialties of participating trial investigators included cardiovascular medicine, endocrinology, hepatology, infectious diseases, oncology, psychiatry, and rheumatology.

We identified several key themes in the study data relating to factors that influence clinical trial reporting: (1) investigator incentives, (2) publishing negative findings in journals, (3) the role of research institutions, (4) nonindustry funder policies, (5) regulating clinical trial reporting, and (6) other factors, including low recruitment levels, time and resource constraints, and views of clinical trial reporting. These themes are presented below, along with selected quotations from trialists (T1-T17), research administrators (A1-A3), and REB members (R1-R3).

Investigator incentives

Accounts from several interview participants suggested academic incentives to publish are stronger for positive than for negative trials due to funding opportunities, promotion, bonuses and recognition. An oncologist described how a positive trial may be more likely to lead to additional research funding: “If I have a positive . . . phase 2 study, that may well lead to a phase 3 study, which often ends up getting picked up by industry.” (T3) A research administrator and investigator in cardiovascular trials talked about recognition, promotion, and funding: “You're going to get a lot more recognition for a positive trial than you do for a negative trial. And that

recognition is important for your own advancement as far as promotion and tenure purposes, but also advancement in terms of getting further grants.” (A1) Investigators described pressures to publish in prestigious journals, which was linked to promotion and faculty merit bonuses. As investigators commonly felt that positive findings were easier to publish in a high-impact-factor journal, positive trials were associated with not only recognition but also promotion and financial reward.

While reporting trials with positive findings may be more highly rewarded, some investigators felt there were also rewards for reporting trials regardless of the trial outcome. A trialist involved in vaccine research noted that demonstrating novel methods could help lead to funding opportunities, and two investigators described the need to demonstrate a good publishing record to attain future funding. Similarly, while some investigators commented on the emphasis on publishing in prestigious journals, a few investigators indicated that the number of articles an investigator had published would show academic productivity, which could help lead to promotion or be a contributing factor in merit bonuses.

When asked about the possibility of changing incentives that may favour reporting positive trials, some investigators suggested that research institutions could play a role. An oncologist suggested that whether trials have been reported could be considered at the time of a faculty member’s annual review and could be tied to promotion. Similarly, an investigator in psychiatry suggested that reporting practices could be linked to “the system of rewarding the researcher for the work done,” such as withholding bonuses when findings are not reported. (T17) Two researchers indicated that changing the culture or communication within their research institutions could be beneficial, such as recognizing negative trials, rather than primarily positive findings, in faculty or hospital newsletters.

Publishing negative findings in journals

Many trial investigators felt it was more difficult to publish a negative trial than a positive trial, and several also believed it was more difficult to publish negative findings in a journal with a high impact factor. Some investigators noted that certain journals have policies to publish negative trials, or to not reject manuscripts based on importance, or that they had not had difficulty publishing negative findings. However, the challenge of publishing negative trials, particularly in prestigious journals, was a common theme. This was reflected in the comments of a research administrator who is also an investigator in cardiovascular trials: “I would like to stress that it can be sometimes extremely difficult to publish a negative study. . . . We did a study on a new compound, and the study was, I think, extremely well-conducted . . . but it came out to be negative, and all the big journals just weren't interested.” (A1) One investigator commented on the reason negative trials may be rejected for publication, based on her experience as a reviewer: “I'm a reviewer on many journals, and if there's no value add, trials aren't published. So they're not going to take a clinical trial if there's no value add It's not interesting. It doesn't change clinical care, it doesn't provide any extra information.” (T12) Given investigator perceptions of the difficulty of publishing negative findings in journals, it is notable that some interview participants highlighted the value of reporting in trial registries.

Role of research institutions

Investigator and research administrator accounts suggested their universities and research institutions tended to lack established, proactive policies and practices to ensure trial findings are reported. When asked whether his research group had any policy related to clinical trial reporting, an oncologist said he was not aware of one, and added: “Based on my past experience,

there is nobody making sure that my work is published.” (T3) One administrator was involved with efforts to promote trial reporting through what he referred to as a “soft approach,” including an initiative to monitor whether registered trials were reported and remind investigators about trials with unreported results, and a pilot project facilitating the use of protocol development software that would make it easier to report findings within ClinicalTrials.gov. (A2) However, these efforts were preliminary and hindered by a lack of guiding policy and a lack of resources.

In contrast, a few oncologists described a more established, proactive approach toward promoting trial reporting at a national group which centrally facilitates cooperative group trials. This approach includes monitoring timelines and the possibility of transferring responsibility for writing a manuscript to another investigator if the principal investigator does not move forward with timely reporting. This process was perceived to be effective in ensuring reporting of at least most trials. One investigator suggested the national group needed to ensure trials were reported in order to secure funding renewals. In effect, the success of the national group’s approach may in part reflect the important role that research funders may play in incentivizing clinical trial reporting.

Interview participants varied in their views about whether research institutions could do more to ensure trials are reported. Among those who thought research institutions could do more, specific suggestions included research institutions monitoring whether trials are reported and clinical research units doing an annual audit of reporting practices. However, some felt universities are not well-positioned to help ensure clinical trial reporting, due to the need to respect academic independence, the challenge of enforcing reporting requirements, and concerns that too many rules might hamper research.

The comments of one administrator suggested research institutions may be unlikely to address the issue of unreported trials on their own, but might act in response to external pressure or policy creating the incentive for them to take action. The administrator’s institution was sensitive to “reputational risk of being identified as a nonpublisher” by the AllTrials campaign, but he highlighted it was difficult to convince his institution to dedicate resources to consistent monitoring of clinical trial reporting without further external pressure: “That’s where I’d like to see us shore that up a bit more, but with 30 other competing priorities—without either media attention or a federal policy telling you have to do something—it slips.” (A2)

Nonindustry funder policies

Research administrator accounts suggested nonindustry funders are in a position to influence reporting for trials they fund. One administrator highlighted that results of National Institutes of Health–funded clinical trials must be reported within ClinicalTrials.gov and nonreporting could be subject to enforcement actions. He suggested that if CIHR required investigators to have reported findings from past trials in order to access future grants, this might change reporting practices. Similarly, another administrator commented that if CIHR required trial results to be reported as a condition for universities to hold CIHR funds, universities would become proactive in helping to ensure results from grant-funded studies were reported.

When contacted for this study, a written response from CIHR highlighted the agency would require grant recipients to publicly report clinical trial results with a specific timeframe and noted penalties for noncompliance were under discussion. In addition, CIHR intends to require funding applicants to provide results to date for all previous clinical trials in which they were the principal investigator. (CIHR’s full reply is available in the **Appendix B**.)

Regulating clinical trial reporting

Several investigators were supportive of regulators playing a role in ensuring clinical trials are reported. While Health Canada has not introduced clinical trial reporting requirements similar to those in force in the US or the EU, some investigators felt that requiring timely reporting within a trial registry would be a reasonable measure to help ensure dissemination of trial results. When asked about this type of requirement, one oncologist responded: “There should be some mechanism to ensure that . . . once your primary endpoint is met, then it's reported within a year.” (T12) An REB member felt it would also be reasonable to include potential fines in regulatory measures, as has been done in the US, as a consequence for failing to report results within a registry within the required time. However, some investigators were uncertain about whether Health Canada should play a role in ensuring clinical trials are reported, due to concerns about feasibility or whether it was important to address the issue of unreported trials.

Other factors relating to clinical trial reporting

Low recruitment levels

Some interview participants mentioned that trials which are unable to recruit many patients may not be published. An oncologist described a phase 3 trial he had been involved with that was stopped due to low recruitment and not published. The trial involved several centres in Canada, and the trialist stated that it had been difficult to recruit patients because the trial was slow to open, although he suggested that the national group coordinating the trial had adjusted its practices since to address this problem. The slow opening of the trial was problematic, he believed, because some investigators at participating centres lost interest in the trial and decided

to recruit patients to a competing trial they were also participating in. He also noted that the national group coordinating the trial has shifted over time to not keeping trials open for recruitment as long, because the field changes quickly and it may not be fiscally responsible.

Other investigators noted that it can be difficult to make inferences from or publish an incomplete trial. For example, another oncologist mentioned that some phase 3 trials with low recruitment rates may not be published for this reason: “There are phase 3 studies that never get completed—the accrual rates weren't as good as we thought they would be, there are studies that just never reach their end point. . . . You have a lot of trouble publishing, so that may not get published.” (T3)

Time and resource constraints

Some investigators highlighted that a lack of time or resources may be a factor contributing to nonreporting or delays in reporting. A couple of investigators suggested small investigator-initiated trials undertaken with minimal resources are at risk of nonpublication due to a lack of resources or “protected, dedicated time.” (T8) Two other investigators mentioned that the pressure to continually write grants and move on to new projects can make timely reporting difficult.

Views of clinical trial reporting

Several investigators felt it was important to address the issue that the results of many clinical trials are not reported in a journal or trial registry. Concerns expressed regarding unreported trials included avoiding duplication of research or waste of resources, avoiding publication bias, and disseminating information on safety concerns. However, several investigators expressed uncertainty or ambivalence about the importance of addressing the issue of unreported trials. A few noted that they were uncertain about the extent of the problem or how

much attention it required. A couple of investigators felt reporting trial results was important, but expressed skepticism about the value of trying to ensure that all trials are published. An oncologist noted that he was of “two minds.” He felt it was important to publish trial results for ethical reasons, but added: “My other view is that it didn't get published for a reason. Negative results, didn't really matter, nothing to learn from it per se. There should be some information somewhere about that trial If somebody tries to go back and do the same thing, they know not to.” (T1)

4.4 Discussion

Several factors have contributed to nonpublication and publication bias in clinical trial research in Canada. Trial investigator accounts suggested some trials are not reported due to investigators placing a greater value on positive trials or perceiving it is less important to publish certain negative findings. However, a core theme emerging from this study is that reporting practices are shaped by incentives within the research system which favour publication of positive over negative trials. Investigators are discouraged from reporting by experiences or perceptions of difficulty in publishing negative findings, while they are rewarded for publishing positive findings in various ways. Publication of positive trials may be more likely to lead to funding from industry sponsors and nonindustry funders. Research institutions play a role in incentivizing publication of positive trials, by rewarding researchers who attract funding and publish in prestigious journals, through promotion, bonuses and recognition. Overall, policies and regulatory measures to promote trial reporting have been too weak and inconsistent to counterbalance the prevailing incentives which lead to nonpublication and publication bias. Research institutions tended lack proactive policies and practices to help ensure trials are

reported. CIHR requirements to report clinical trial results have not previously specified a timeline for reporting. While regulatory requirements to report findings in registries similar to those in other jurisdictions could help promote reporting of trials, such measures have not been adopted in Canada.

Comparison with other studies

From early studies to more recent systematic reviews, studies examining reasons for nonpublication of medical and health-related studies have emphasized the role of investigators in nonpublication.^{4,14,35,114,186,187} This is reflected in two systematic reviews of studies which surveyed investigators on reasons for nonpublication.^{14,35} One suggested investigators are primarily responsible for nonpublication, as the majority of unpublished medical and health-related studies have not been submitted for publication.³⁵ The other stated that investigators rather than journals are responsible for nonpublication of biomedical studies, because the expectation of journal rejection was not among the most common reasons given by investigators for nonpublication.¹⁴

In contrast, our study highlights that powerful incentives relating to recognition and career advancement may underlie investigator decisions on whether to submit a trial for publication. Among a range of other influences on clinical trial reporting, journals may play a role in shaping investigators' reporting practices. A randomized controlled trial of reviewer behaviour suggested reviewers favour studies with positive results,³⁴ although this finding differed from earlier observational studies of journal editorial decisions.⁹⁵⁻⁹⁷ On balance, these findings suggest journals may contribute to publication bias but likely play only a small direct role in the problem.

However, any bias in the editorial review process of journals might also have indirect influence by deterring some investigators from submitting negative trials for publication.

Previous articles have highlighted aspects of academic incentives relating to clinical trial reporting. Articles have noted that assessment of researchers for academic hiring and promotion often emphasizes the number and citations of articles published and publication in high-impact-factor journals^{48,110} and that research funders may rely on the impact factor of an investigator's publications as an indirect measure of research quality.^{47,113} A critique of how value is assessed in biomedical research argued that scientists are rewarded for publishing novel, significant results, leading to nonpublication of high-quality studies with negative results.⁴⁶

In our interview study, the accounts of investigators and others connected to trial research associated positive trials with funding opportunities, promotion, bonuses, and recognition. This lends empirical support to previous critiques of academic incentives while providing additional insights. We found that positive trials may be more likely to lead to funding not only from granting agencies but also from industry sponsors. Our findings highlight that research institutions contribute to incentivizing publication of positive trials through not only promotion and hiring practices but also recognition of positive results in communications such as faculty and hospital newsletters. In addition, our study indicated research institutions tended to lack well-resourced, proactive policies to ensure trials are reported in journals or registries.

While our study highlights the association between academic incentives and nonpublication relating to results for the primary outcomes of trials, an Institute of Medicine report discusses academic incentives relating to publication of findings from secondary analyses of trial data.¹⁸⁸ The academic reward system arguably disincentivizes sharing of trial data, because “academic and industrial success depends on published output” but sharing data could allow others to

publish results based on secondary analyses before the those who have conducted the trial have had the opportunity to do so themselves.¹⁸⁸ When clinical trial data are not shared, this may delay publication of secondary analyses or lead to nonpublication of such analyses.

Policy implications

Policy actions to address nonpublication and publication bias may require changing incentive structures.^{17,46-48,148,165} This could involve research institutions adopting performance metrics that include an assessment of whether investigators have fully disseminated their research findings in journal articles or trial registries.^{17,46-48,148} Providing academic credit for posting results in a trial registry could help incentivize more timely reporting in registries.¹⁶⁵ It may also be valuable for research institutions to implement programs to support researchers to report results in trial registries in a timely manner. This could be modelled on strategies used at some US medical schools to improve compliance with regulatory requirements to report clinical trials, which include dedicating resources, communicating with investigators, providing support and training, and monitoring compliance.^{173,174,189}

While research institutions have a role to play in helping ensure trial results are reported, our study suggested research institutions may be unlikely to address the issue of unreported trials in the absence of external pressure to take action. Moving toward full reporting of clinical trial results will likely depend on effective regulatory requirements to report trial results. Although compliance with regulatory requirements in the US and EU to report applicable clinical trial findings in trial registries has been low, it could likely be improved with consistent monitoring and enforcement of financial penalties.^{44,45} The FDA issued a notice of noncompliance to a trial sponsor for the first time in April 2021, and has stated it may pursue enforcement actions as

necessary to help ensure trials are reported by responsible parties.¹⁵¹⁻¹⁵³ Canada and other jurisdictions lacking similar regulatory requirements could promote clinical trial reporting by adopting such requirements, accompanied by monitoring and enforcement.

Nonindustry funder policies can play a role in helping ensure full reporting of trials through mandatory reporting requirements and guidelines for peer review of funding applications.^{47,113,170} As reporting requirements with timelines and noncompliance measures are more likely to be effective, it is welcome that CIHR publicly committed to requiring grant recipients to report trial results within a specific timeframe¹⁶⁶ and indicated penalties for noncompliance were under discussion. Similarly, CIHR's intention to require funding applicants to provide the reporting status of previous trials¹⁶⁶ could serve as an incentive for full reporting of trials. In a December 2020 statement, CIHR committed to publish new policy requirements in the following year regarding a 12-month timeframe for public disclosure of clinical trial results and the requirement that grant applicants provide the reporting status of previous trials.¹⁶⁶ CIHR has also signed the San Francisco Declaration on Research Assessment (DORA), which recommends that funding agencies should “clearly highlight . . . that the scientific content of a paper is much more important than publication metrics or the identity of the journal in which it was published.”^{167,190} While this principle is reflected in some CIHR grant evaluation criteria,¹⁶⁸ it would be valuable to ensure it is more clearly and consistently communicated in peer review guidance available to reviewers of applications for clinical trial funding.¹⁶⁹

Strengths and weaknesses of the study

The qualitative design of the study allowed for an open-ended inquiry into nonpublication and publication bias in clinical trials through the accounts of clinical trial investigators and others

connected to trial research. It was strengthened by the inclusion of participants from different provinces and trial investigators from a range of medical specialties. However, the study had limitations. The study included individuals involved in the conduct, administration or ethical review of trials, but did not include representatives of funders, journals, or regulators. Individuals who agreed to be interviewed might differ from those who did not, such as placing a higher value on full reporting of trials. As the study involved only participants in Canada, it is uncertain to what extent our findings are generalizable to other jurisdictions.

Future research

It could be useful to conduct further research to learn more about clinical trial investigator views on policies that might be adopted by research institutions, ethics boards, funders or regulators to address nonpublication.

Conclusion

While a range of factors contribute to nonpublication and publication bias in clinical research, our study suggests clinical trial reporting practices in Canada are shaped by incentives which favour publication of positive over negative trials. Canadian universities and research institutions could help change incentives by more widely adopting performance metrics that emphasize full reporting of trial results in journals or registries. Health Canada could also play a central role in changing incentives by adopting regulatory measures to require timely reporting of results within a recognized clinical trial registry.

Chapter 5: Reporting clinical trial findings as an ethical responsibility to research participants

5.1 Introduction

A systematic review indicated approximately 4 in every 10 randomized controlled trials included in trial registries were not reported in journal articles after a period of 2 or more years from study completion.³ Similarly, other systematic reviews have suggested that clinical and biomedical studies are often not published.^{1,2} Studies have also found low compliance with regulatory requirements for timely reporting of clinical trial results within ClinicalTrials.gov and the EU Clinical Trials Register.^{44,45}

Advocates of full reporting of clinical trials have argued nonpublication betrays trial participants and violates an implicit contract between participants and researchers.^{19,40-43} They reason that when individuals agree to participate in trials, they expect their participation will contribute to medical knowledge and help future patients. When trial findings are not reported, this expectation is not fulfilled. More fundamentally, as individuals may reasonably expect trials to contribute to knowledge when deciding to participate in a trial, nonreporting of clinical trials may undermine informed consent.^{19,43}

Arguments that clinical trial investigators have a duty to trial participants requiring them to report findings are strengthened by previous research suggesting that motivations for participation in trials include altruism.³⁶⁻³⁹ In addition, a survey of non-critically ill patients in an emergency department setting found that most felt it was important to make clinical trial results publicly available.¹¹⁸ However, trial participant views of the importance of reporting research findings and trial investigator views on the responsibility to report findings are unclear.

We conducted a qualitative interview study to investigate clinical trial reporting in Canada. The analysis reported in this chapter aimed to understand how the experiences and views of trial participants, trial investigators, and others relate to whether researchers have a duty to trial participants to report research findings.

5.2 Methods

Study design

We conducted a qualitative interview study using a grounded theory approach.^{49,50} Methods included semistructured interviews, coding data with sensitivity to emergent concepts, and inductive analysis to explore interview participants' experiences and views. Our research team for this project included a clinical trial investigator (SG), an expert in qualitative methods (GG), a health research analyst (RM), and researchers in epidemiology and health policy (BM, ML, and CD).

Participants and sample

The study aimed to include clinical trial participants, clinical trial investigators, clinical research coordinators, research administrators, and research ethics board (REB) members. Interviews with trial participants and trial investigators were the primary focus on the study, and this was complemented with a smaller number of interviews with others connected to clinical trial research to provide additional perspectives. Inclusion criteria are listed in **Table 1**.

We primarily used a purposive sampling strategy. We invited participation from trial participants who varied in demographic characteristics and had participated in trials for a range of treatments, trial investigators in diverse medical fields, and participants from different provinces in Canada. Snowball sampling was used to gain referrals to additional trial

investigators and REB members who might be asked to participate. The study received ethical approval from the University of British Columbia Behavioural Research Ethics Board (H18-03458) and the University of Alberta Health Research Ethics Board (Pro00096201), and all participants provided informed consent.

Recruitment

Strategies to recruit past trial participants included advertising in a free newspaper and contacting clinical research coordinators and managers for assistance. We emailed or telephoned 11 individuals who expressed interest following the advertisement or consented to be contacted (10 participated and 1 did not respond). We identified other types of participants through online sources (ClinicalTrials.gov, Canadian Clinical Trials Asset Map database, and websites of research institutions and REBs) and referrals. We invited participation from 61 trial investigators by email (17 investigators participated, 2 responded but were unavailable for an interview during the study, 36 did not respond, and 6 declined). Investigators who declined stated they were too busy (1), not interested (1) or lacked relevant experience (4). A clinical research coordinator who worked with a participating trial investigator also volunteered to take part in an interview. In addition, we emailed 12 research administrators (3 participated and 9 did not respond) and 15 REB members (3 participated and 12 did not respond). Trial participants and trial investigators were eligible to receive a \$50 honorarium for participation.

Data collection

Participants took part in semistructured interviews from March 2019 to April 2021. Interview guides for each type of participant were used. (**Appendix A**) Interviews were primarily based on open-ended questions and allowed for exploration of unanticipated issues. Data collection

included initial interviews in person or by telephone with 34 participants and follow-up telephone interviews with 4 participants to collect additional information. The duration of interviews was approximately 45 to 60 minutes for initial interviews and 20 minutes for follow-up interviews. In-person interviews were held in a public library meeting room or at the interview participant's workplace. A transcriber prepared transcripts for analysis from audio recordings of each interview. RM conducted the research interviews and coded the interview data. Data collection continued until the data allowed for a detailed analysis addressing the study's research questions.

Data analysis

Interview transcripts were analyzed using ATLAS.ti (version 8), including coding and deriving themes from the data. Analysis included initial coding with an open-ended approach, followed by focused coding to retain and develop key themes for analysis.⁴⁹ Collection of data from different types of participants allowed for triangulation of data during analysis.⁵² In addition, we aimed to strengthen the reliability of the study by providing illustrative quotations from interviews.

Role of funding source

This study was funded with unrestricted research funds provided by the British Columbia Ministry of Health to the University of British Columbia. The funder had no role in the design, conduct, or reporting of the study.

5.3 Results

Overall, 34 participants took part in the study, including 10 clinical trial participants, 17 clinical trial investigators, 1 clinical research coordinator, 3 research administrators, and 3 REB

members. (**Table 2**) The study included participants from the Canadian provinces of Alberta, British Columbia and Ontario. Past trial participants included men (3) and women (7), whose ages ranged from 38 to 77 years at the time of their initial interview. They had taken part in trials of 6 months to 5 years in duration, testing treatments for cardiovascular disease, *C. difficile* infections, chronic pain, diabetes, eye disorders, and multiple sclerosis. Among interview participants who were involved in the conduct, administration or ethical review of trials, some spoke about both conducting trials and playing a role in research administration or reviewing ethics applications. Trial investigators who took part in the study had conducted trials in cardiovascular medicine, endocrinology, hepatology, infectious diseases, oncology, psychiatry, and rheumatology.

Our study results are presented below by theme. This includes themes relating to trial participant experiences and views (motivations for participating in a trial and trial participant views on reporting research findings), accompanied by quotations from trial participants (P1-P10). The findings below also include themes related to accounts from those involved in the conduct, administration or ethical review of trials (views on clinical trial reporting as a responsibility to research participants, linking clinical trial reporting to informed consent, and the role of research ethics boards), presented with quotations from trial investigators (T1-T17) and REB members (R1-R3).

Motivations for participating in a clinical trial

Most trial participants stated they were motivated to take part in clinical trials in part to help future patients, although this was not always the case. One trial participant, who joined a trial to access treatment after suffering from a sudden deterioration of her vision due to an eye disorder,

described feelings of guilt she experienced due to having joined the trial for her own benefit rather than to help others: “Many of the technicians that I saw, and the doctors, would often say to me how grateful they were for my participation in this research. So after a while I kind of felt guilty, but I was only in it initially for myself.” (P2) More generally, patients who were in more urgent need to improve their health condition were more likely to identify access to treatment as their primary reason for participating in a trial. However, they also often wanted to help future patients and conceived of their participation as an act of solidarity with others like them. A patient who had experienced a recurring *C. difficile* infection recalled that at the time of joining a clinical trial she had told family members: “Nobody should have to suffer this way, and if there's anything that I can do to help medical science move forward so that other people don't have to suffer like this in the future, I'm all for it.” (P6) Patients with a less urgent need to improve their health condition were more likely to identify helping future patients as their primary reason for joining a trial. For example, a patient with type 1 diabetes recalled that she had joined multiple clinical trials over time because she “figured if there isn't research being done to help people, then nothing is ever going to improve.” (P7)

Trial participants typically had multiple motivations for participating in a trial. An individual who had taken part in a drug trial for secondary prevention of cardiovascular events was interested in advancing medicine and in being part of something important: “If you can make medicine better and be a part of that, it's pretty nice to be able to be involved in something like that.” (P8) He also participated out of interest and to have greater access to specialized care. A patient who had taken part in trials of treatments for type 1 diabetes stated that she was motivated to participate in research to help other patients and to help her health provider, while adding that another part of her motivation was access to free diabetic supplies. A patient with

relapsing-remitting multiple sclerosis chose to take part in a trial when he needed to switch treatments following a relapse. When asked about his motivation for participating, he noted it was convenient to have access to free treatment rather than having to go through his health insurer and he appreciated the additional health monitoring. He was also interested in advancing medicine, but recognized that medical advances may take time: “I know that progress is probably going to be very incremental at best, but any advancement is better than nothing, and we can always make a discovery along the way.” (P10)

Contributions of research participants in clinical trials

An important way that clinical trial participants contribute to research is by assuming the risks inherent in trials. A patient who had taken part in a 2-year trial was concerned about the possible cancer risk she was informed about prior to her participation and was relieved afterwards when she learned she had been in the control group. While most past trial participants did not believe they had suffered adverse effects from study treatments, a patient in a trial of pain medication stated that she had experienced mental confusion and fatigue that at times left her unable to function. In addition, research participants contribute to clinical trials through activities such as undergoing medical tests, participating in surveys or interviews about health status, and tracking measures such as blood sugars, mood or pain levels.

Some trial participants felt they had benefited from the study treatment, even in a life-changing way, and some felt they had benefited from receiving a higher level of care. However, one trial participant felt the benefit she received from the treatment was disappointing and another was uncertain whether he had benefited, which highlights it is possible for trial participants to receive little or no direct benefit from their participation.

Trial participant views on reporting research findings

Most past trial participants felt it was important for the results of clinical trials to be published. Trial participants stated various reasons they felt publishing research findings was important. Some suggested if results were not published, this would represent a waste of time or resources. A patient who had participated in a trial to test a treatment for *C. difficile* felt it was important to avoid wasting the effort and resources invested in a trial: “If we're doing the work, spending the dollars and not using that information to further medical science, then what was the point of doing all that work in the first place?” (P6) Another patient, who had taken part in a trial to test a treatment for relapsing-remitting multiple sclerosis, emphasized the importance of reporting results to help future patients: “If you don't publish . . . then how is it to be paid forward to help other people?” (P5) Some trial participants stated it was important to publish trials to learn from negative or incomplete trials, inform the medical community, demonstrate transparency, and improve future research. However, not all patients stated that publishing trial results was important. A patient who had been in a trial of a treatment for an eye disorder felt it was hard for her to judge whether it was important to publish results from a trial suggesting a treatment did not work. When asked about the importance of reporting the results of clinical trials, another patient spoke about how he would feel about publication of the results of the cardiovascular trial he had participated in rather than about the importance of reporting in general: “I think it would be nice if [the results] were published, because then—I mean, I would feel better. I don't know about any other participant, but I would feel a little better knowing that my participation helped in something.” (P9)

When some participants described the value of clinical trial reporting, they highlighted the contribution of trial participants to research. A patient with type 1 diabetes felt it was important

to publish trial results, “because of a lot of effort that a lot of people put into it—not just the researchers, but the people that were participating in the trial.” (P7) Similarly, another trial participant said she felt it was important to publish trial results in part because “people were gracious enough to be part of it.” (P2) One trial participant reflected that she was quite willing to be a “guinea pig”, but she would feel “cheated” if the trial she had participated in were not published, because she had participated “not just for me.” (P5) Taken together with statements from a larger number of trial participants that they had participated in part to help other patients, these comments suggest reporting the results of trials is important as a form of reciprocity between researchers and trial participants. However, none of the trial participants was aware of whether the results of the trial they had participated in had been published, although in some cases the trials they had taken part in were either ongoing or so recent that it would be reasonable that results might not have been published at the time of their interview. In effect, reciprocity between trial participants and researchers may require reporting of trial results, but trial participants might often not be able to observe whether this is fulfilled.

Views on clinical trial reporting as a responsibility to research participants

Among investigators, administrators and REB members interviewed for this study, many felt researchers have an obligation to trial participants to report the results of clinical trials. Comments highlighted that trial participants contribute their time and expose themselves to risk, yet may not directly benefit through their participation. Several comments suggested reporting results is necessary as a kind of reciprocity, or to fulfill an implicit agreement, between trial participants and researchers. A trial investigator who studied treatments for infectious diseases felt publishing was important as a responsibility to trial participants: “Well they've spent their

time—and then also risk. There's a potential risk of entering a clinical trial, so I think as researchers we have a responsibility to hold true to their commitment and altruism to enter into a clinical trial.” (T16) An endocrinologist who conducted clinical trials said: “I think most people understand that this may or may not benefit them, but hopefully this will benefit society. . . . If it's not even published, then we're not fulfilling our side of the bargain.” (T14) Similarly, a couple of investigators suggested that a “contract” between participants and researchers obligated researchers to report results. Notably, the chronology of this reciprocity or “bargain” involves the trial participants contributing their time and exposing themselves to risk without knowing whether researchers will fulfill their implicit obligation to report the research findings. This was reflected in the comment of one trialist, who noted: “People have volunteered, given their time, given their samples *in good faith* that some science is going to come out of it.” (T7, emphasis added)

Some trial investigators felt a responsibility to trial participants to publish trials results existed but it could be difficult or less important to publish in certain circumstances. A research administrator who conducted trials reflected on a trial which had attracted very few participants: “We kind of gave up the study for futility purposes, and that study never got published. It was just not enough data to make any conclusions. So there's an example where, okay, it didn't work out—but I could see why it might not get published.” (A1) When asked about whether there is a responsibility to trial participants to publish results, he said: “I think whenever possible there is a responsibility to participants, but you can't always fulfill. that.” A cardiovascular investigator, who spoke about the difficulty of publishing incomplete trials, stated: “To me, not publishing is unethical, but I can see some situations where it's just not possible.” (T10) He also suggested trials stopped early following a decision by an industry sponsor to halt development of a drug

could be less important to publish due to a lack of statistical power and lack of relevance.

However, he felt that in some circumstances the responsibility to report was compelling: “By the time you get to hundreds or thousands of patients involved . . . it's unethical not to do it because of the patient contribution.”

Linking clinical trial reporting to informed consent

Several investigators linked an obligation to report trial results in a journal or trial registry to informed consent. In some cases, consent forms signed by trial participants actually indicate research findings will be published. More generally, trial participants may reasonably expect or be told a trial will contribute to medical knowledge. An investigator in hepatology trials suggested this requires researchers to report their findings: “We specifically say the benefit will be greater knowledge to the scientific and medical community, which will hopefully benefit other people in the future. So if we're not sharing the results of the study, then that's not true. . . . We are not honouring that consent.” (T15)

When trials showing drug harms or a lack of efficacy, including early phase trials, are not reported, this may also undermine informed consent in future trials. An investigator noted that trials identifying safety concerns may provide information relevant to future trials of similar drugs. Although another investigator was less concerned about this issue because drugs in the same class would not necessarily be associated with the same adverse effect, in some cases information about harms of one drug in a class is deemed important enough to add to consent forms used in trials of drugs in the same class. Similarly, an investigator and an REB member each highlighted that publishing trials showing harms may inform other trialists that trials of the same or similar drugs would expose patients to excessive risk. In addition, the REB member

commented that nonpublication of negative trials may lead to redundant research which unknowingly involves patients in trials of drugs lacking efficacy.

Role of research ethics boards

Accounts of interview participants suggested REBs did not typically play an active role in monitoring trial reporting or helping ensure trial results are reported. Among REB members, one felt REBs could monitor reporting of local trials but was concerned it might be too complicated to extend monitoring to international trials. The other two REB members interviewed were asked whether REBs could periodically audit whether trials the ethics boards had approved were reported in trial registries and publicly report their audit results. One REB member felt this would be valuable but highlighted REBs are overburdened and lack the necessary resources for this work. The other REB member, who was a university-based trial investigator, suggested it would be reasonable for REBs to audit trial reporting, if this were an institutional priority and adequately funded: “If the university as a whole feels that it is important, then we can advocate for it, and make the university pay for this decision and then do it.” (R2)

5.4 Discussion

The accounts of trial participants, trial investigators, and others connected to clinical trial research suggest that when researchers enroll patients in clinical trials there is often an implicit understanding among researchers and trial participants involving an obligation to report research results. Most trial participants were motivated to enter clinical trials in part to advance science, and most felt that reporting the results of clinical trials is important. Trial participant accounts suggest their contributions are part of a reciprocal relationship involving the expectation that research will advance medical knowledge. Similarly, comments from trial investigators suggest

that reporting trial results is part of reciprocity with trial participants and is a necessary part of honouring informed consent. In addition, when trials are not reported, this may undermine informed consent in subsequent trials by withholding information on harms or efficacy relevant to informed decisions on whether to conduct or enroll in future trials of similar drugs.

Our finding that many trial participants were motivated to join trials in part to help future patients is consistent with previous studies on reasons for participation in trial research.³⁶⁻³⁹ Our study adds that even patients who are strongly motivated to participate by the opportunity to access treatment may feel it is important to help future patients out of a sense of solidarity with others like them. In fact, trial participants typically have multiple motivations for joining a trial, which vary among participants but may include access to specialized care, access to free medication or medical supplies, helping one's health provider, and interest in the research.

A survey of non-critically ill patients in an academic emergency department in the northeastern United States (US) found that most felt it was important to report trials results.¹¹⁸ Our study indicated most individuals who had recently taken part in a clinical trial felt it was important to report trial results, while highlighting trial participants may view their own contributions as part of a reciprocal relationship involving the expectation that trials will contribute to medical knowledge. However, this reciprocity which involves a responsibility for researchers to report trial results may be weakened for various reasons. First, trial participants may often not find out whether trial results are published by the researchers, which might diminish a researcher's sense of the obligation to publish as a responsibility to the trial participants. Second, trial participants might be unlikely to question whether results have been reported, due to losing contact with researchers who are not their regular health providers,

respect for the authority and expertise of the researchers, or gratitude for other benefits received in the trial (such as access to treatment or greater medical attention).

Importantly, our study strengthens empirical support for arguments that when trial results are not reported, this violates an implicit agreement or contract between researchers and participants and undermines informed consent.^{19,41-43} Trial participants may consent to enter a trial with the understanding that research will benefit future patients. However, this consent is not respected when trial results are not reported and this potential benefit is not fulfilled. In effect, the core ethical principle of respect for persons is undermined, as informing trial participants of the risks and benefits of research is part of respecting their autonomy as research participants.^{119,120}

Policy implications

This study found that both trial participants and trial investigators may feel clinical trials involve an implicit understanding that trial results will be reported. Despite this, results are only published for approximately 4 in every 10 randomized controlled trials, and studies have found low compliance with regulatory requirements to report results in trial registries.^{3,44,45}

Investigators in this study indicated consent forms may indicate that results will be reported, but this appears to be uncommon.¹⁹¹ It could be valuable for REBs to require a standard clause in consent forms to indicate trial results will be reported in a journal or registry. This would serve to promote the full reporting of trials and communicate the importance of reporting results for fulfilling informed consent.

REBs could promote reporting of clinical trials through periodic audits of clinical trials they have approved to contribute to quality improvement and increase accountability of research institutions and sponsors for reporting practices.¹⁷² However, REBs are already overburdened,

and they would likely only be able to play this role if their responsibilities and budgets were adjusted to allow for this. Alternatively, REBs could assist universities and other research institutions to implement programs to monitor and support reporting of clinical trials. For example, programs at some US medical schools to improve compliance with regulatory requirements to report clinical trials have relied on access to data from institutional review boards to help monitor clinical trial reporting.^{173,174}

Stronger regulatory measures could improve clinical trial reporting policy or practices of research institutions, sponsors and individual investigators. Canada currently lacks regulatory requirements to register and report clinical trials in a registry or journal. Phase 1 trials are largely excluded from current regulatory reporting requirements in the US and European Union,^{45,165} whereas our study highlights reporting early phase trials is necessary for fulfilling informed consent. The effectiveness of mandatory reporting requirements depends on expanding their scope to cover all clinical trials of drugs and biologics, enforcing reporting requirements,^{44,45,153} and adoption in additional jurisdictions, including Canada.

Limitations

Our study has limitations. While we included past trial participants who had taken part in trials for a range of medical conditions, our sample did not include participants from some common types of trials such as oncology trials. Consequently, it is uncertain whether our findings regarding trial participants are generalizable to participants in all types of trials. As the sample of past trial participants interviewed for this study was small, caution is warranted in generalizing from these interviews. However, this limitation was mitigated by triangulation of findings among different types of participants regarding reciprocity between researchers and trial

participants and the responsibility to report results. More generally, it is not clear to what extent our findings apply to clinical trial settings outside Canada, as experiences and views of clinical trial reporting might vary due to differences in funding, policy or health care systems. Among trial investigators, research administrators and REB members contacted to participate in this study, the proportion who did not respond or declined to participate was high. It is possible that attitudes toward clinical trial reporting differed in those who participated compared to those who did not take part in the study.

Conclusion

The views of trial participants, trial investigators, and others connected to clinical trial research in Canada suggest that researchers have an obligation to research participants to report clinical trials results and that reporting of results in registries or journals is necessary for honouring informed consent. REBs could play a role in ensuring clinical trials are reported by auditing whether trials they have approved have been reported or by assisting research institutions to monitor and support reporting of clinical trials conducted at their centres. Future studies could investigate views on clinical trial reporting in other countries.

Chapter 6: Clinical trial transparency in the context of strategic interests and power

Chapters 3 to 5 describe how nonpublication and publication bias may occur and how the ethical responsibility to report trials is understood by trial investigators, trial participants and others connected to clinical trial research. Drawing on themes described in these earlier chapters, this chapter explores why nonpublication and publication bias occur in clinical trial research, while further considering ethical implications. The analysis described in this chapter considers how the strategic interests and power of various actors involved in the process of trial reporting lead to their actions and omissions with respect to trial reporting, which in turn bring about partial transparency of clinical trial research. This chapter describes strategic interests and power relating to clinical trial transparency, the dynamics of changing policy and practices relating to trial transparency, ethical implications, and the transparency of individual patient data and clinical study reports, and it concludes with a chapter summary.

6.1 Strategic interests and power relating to clinical trial transparency

Much of this thesis has focused on how the actions and omissions of various actors have led to nonpublication and publication bias. The commercial incentives of industry sponsors, career-related incentives of trial investigators, and research institutions' concern with attracting funding and managing reputational risk have also been highlighted, which speaks to the strategic interests of these actors regarding trial reporting. These strategic interests have provided a partial explanation of why only partial transparency of clinical trial reporting occurs, but additional consideration of both the strategic interests and power of these and other actors could provide a deeper understanding. A summary of the strategic interests of a range of actors, power to

influence trial reporting and other actors, and actions and omissions is provided in **Table 3**. A discussion of the strategic interests and power of various actors in clinical trial reporting is presented below, organized according to the following themes: balancing transparency with other strategic interests, the influence of dominant stakeholders on policy making, ethical obligations without accountability, and advocacy for clinical trial transparency.

Balancing transparency with other strategic interests

While industry sponsors, research institutions, and trial investigators may have an interest in pursuing transparency to advance knowledge and to manage the reputational risk associated with failing to report results, each of these types of actors also has other strategic interests which may lead to nonreporting of trials. Industry sponsors have a commercial interest in selectively reporting trials with more favourable results for their products. Research institutions aim to raise funds from industry and nonindustry funders to ensure their viability in a competitive environment,⁴⁷ which leads them to reward researchers for attracting funds and publishing in prestigious journals. Trial investigators preferentially report trials with positive over negative findings,⁹⁷ which may be more likely to lead to not only funding but also career advancement within their research institutions.

Industry sponsors are in a position of influence over research institutions and investigators, who often have a dependency on industry funding to ensure research programs are viable and conduct research. This allows sponsors to have influence on decisions to report trials in a variety of ways (as described in Chapter 3). Research institutions have some bargaining power with industry as academic centres provide expertise, access to patients, and credibility to clinical research, but this is weakened by their perceived need to compete with other research institutions and non-academic trial sites.⁶⁹ Although Canadian research institutions are concerned with the

reputational risk of being identified as having poor reporting practices, they have not been subjected to a degree of publicity which would cause them to develop policy and programs to help ensure trials are reported. Trial investigators have some control over whether trials are reported in registries or journals, particularly for investigator-initiated trials. However, their behaviour is shaped by powerful career-related incentives created by industry sponsors, research institutions, and others, and they do not always have full control over whether trials are reported.

Journals may also be divided between their interest in publishing high-quality clinical trial research and a strategic interest in publishing novel and significant findings, which might raise a journal's impact factor to build prestige or increase revenue.⁴⁷ Interviews in this study suggested trial investigators may be discouraged from reporting due to their perceptions or experiences of difficulty in publishing negative findings, although the extent to which journals contribute to publication bias is somewhat unclear. Journal editors and reviewers have a gatekeeping role in determining what clinical research is published in journals, which provides some power in the clinical trial reporting system. However, they may also be influenced by industry sponsors, who may provide revenues through purchasing advertising and reprints.⁴⁷

Influence of dominant stakeholders on policy making

While Health Canada as the regulator and CIHR as the primary nonindustry funder of clinical trials in Canada are both in a powerful position to influence clinical trial reporting, neither has a history of strong policies to help ensure clinical trials are reported. While their roles would suggest they have an interest in enhancing the transparency of clinical trials, their history of inaction may reveal other strategic interests. The economic power and prestige of the pharmaceutical industry in Canadian society may allow it to influence the policies of both Health Canada and CIHR. Additionally, research institutions' interests may influence CIHR policy, in

part through the participation of members of the academic research community in the agency's governance. Health Canada and CIHR are influential in setting the context for clinical trial reporting in Canada. However, their policies relating to clinical trial reporting may reflect the interests of industry and research institutions, who could be considered dominant stakeholders.

Although Health Canada has recently adopted a policy of proactively releasing CSRs following regulatory decisions on new drugs and devices,¹³⁹ its previous approach of treating clinical trial information it received from manufacturers as largely confidential and proprietary reflected an alignment with the interests of industry.^{124,125} From 2005, Health Canada has provided information about regulatory approvals of drug and devices in the form of SBDs, which contain information about the summary results of premarket clinical trials, although an evaluation of SBDs found that the clinical trial information they provided was inadequate to aid in clinical decision-making.^{87,133} While Health Canada's move to start proactively releasing CSRs represents a large step toward greater transparency, it was arguably precipitated by a court ruling regarding a specific data request from researcher Peter Doshi (described in Chapter 2).^{139,141} Health Canada's failure to introduce regulatory requirements similar to those in Europe and the US requiring many trials to be reported within trial registries likely reflects its orientation toward the concerns of industry sponsors.

CIHR's history of weak policies regarding clinical trial reporting may reflect an alignment with research institutions and industry. The agency is associated with these interests in part through its governing council, which currently includes a vice president of research and innovation from a Canadian university and in the past has included a vice president of medical affairs from a global pharmaceutical company.^{87,192} CIHR's alignment with industry is also reflected in the language of the 2018 *Tri-council policy statement (TCPS2)*, which is coauthored

by CIHR.¹¹⁹ A section of the TCPS2 on clinical trial agreements requires that research institutions “should ensure that sponsors’ legitimate interests are reasonably balanced against researchers’ ethical and legal obligations to participants and their duty to disseminate data and research findings”, which legitimizes industry sponsors’ proprietary rights over data without protecting investigators’ ability to publish within a specific time period.^{119,193} In 2020, CIHR signaled that it may strengthen its policies, when it signed the *WHO Joint statement on public disclosure of results from clinical trials* and announced it would develop policy guidance including a policy to require CIHR-funded trials to be reported within a specific timeframe.¹⁶⁶ However, CIHR signed on to the statement more than three years after funders such as the UK’s NIHR, and the effectiveness of the agency’s policy in this area will depend on how it is implemented.¹⁹⁴ The agency’s delay in signing on to the WHO joint statement suggests a continued ambivalence toward trial transparency.

Ethical obligations without accountability

This study has highlighted that an implicit agreement may exist between trial participants and trialists involving a duty to report clinical trial results. In some cases, consent forms indicate research findings will be published. More generally, the accounts of some interview participants suggested there is a reciprocity between trial participants and researchers in which the trial participants contribute their time and expose themselves to risk and in return researchers have a responsibility to contribute to knowledge by reporting trial results. As noted in Chapter 5, one trialist captured this when he reflected: “People have volunteered, given their time, given their samples in good faith that some science is going to come out of it.” (T7) Due to the reciprocity noted above and its relevance to informed consent, trial participants have a strong moral claim to assert that researchers must report the results of trials. If this moral claim could be communicated

to the research community and in the larger public sphere, it might be a source of power for trial participants to bring about greater transparency.

This reciprocity between researchers and trial participants and the potential power of trial participants regarding transparency may be weakened for various reasons. Researchers' sense of duty to report results may be diminished because trial participants usually do not find out whether results are reported or not. As the trialist above stated, trial participants have engaged in a reciprocal relationship "in good faith", but as he may imply, there is a lack of accountability for not fulfilling the ethical obligation to report results of trials. Additionally, trial participants may be motivated to join trials in part to help others and have an interest in trial results being reported, but they may often have other motivations as well, such as access to treatment, specialized care, or free drugs or medical supplies. In the language adopted above, they have other strategic interests. Trial participants may not be as likely to seek confirmation of whether trialists fulfill their responsibility to report trials, or advocate for full reporting of trials, in part because they have other interests which have been served in some way, even if they may not have actually benefited from an experimental treatment.

REBs have a role to ensure that ethical principles are respected in clinical trial research, but they may not interpret their role as extending to activities such as monitoring of trial reporting to ensure results are reported. The authority of ethics boards appears to provide some power over sponsors and researchers which could be leveraged to increase transparency. A practical constraint is that their power lies largely in the ability to withhold ethical approval for conducting a trial, whereas reporting is a post-trial activity. This would not prevent REBs from conducting audits of whether trials they have approved are reported in a timely manner and publicly disclosing their findings, which could increase accountability of sponsors and research

institutions for reporting. However, their power to undertake such activities may be limited in that they are overburdened with other responsibilities and tend to lack sufficient resources to do more. As REBs are often affiliated with specific research institutions and have members from those institutions, their strategic interests may be aligned with those institutions and they may hesitate to undertake activities such as audits which could undermine the reputation of their institutions. For-profit REBs might also be unlikely to engage in activities regarding accountability for clinical trial reporting, which would not serve their commercial interests. Ethics boards may require trial investigators to include a plan for publication in their protocols in order to gain ethics approval, but they typically do not have accountability mechanisms in place to ensure sponsors and investigators follow through on their commitment to report research results.

Advocacy for clinical trial transparency

Transparency researchers and advocates could be considered another actor in the system of clinical trial reporting. Individuals and organizations who have pursued research or advocacy on clinical trial transparency have created pressure for change and have played a role in policy changes. In this study, an administrator noted that his university was concerned about “the reputational risk of being identified as a nonpublisher”, based on data produced by the Oxford DataLab and publicized by the AllTrials campaign. Although the magnitude of reputational risk was not great enough to motivate his institution to act, his additional comment that it would likely take further external pressure such as media attention for his institution to change highlights the importance of advocacy for transparency. In the UK, research and advocacy such as the AllTrials campaign, led by the Oxford DataLab and Sense About Science, have drawn greater attention to nonreporting of clinical trial results. This has likely helped bring about the

Make It Public strategy overseen by the UK's research ethics regulator, the Health Research Authority.¹⁹⁵ As part of the implementation of this strategy, the Health Research Authority will automatically register all clinical trials and will monitor whether clinical trials are reported.¹⁹⁶ In the Canadian context, it is worth again mentioning that researcher Peter Doshi, working closely with researchers Matthew Herder and Trudo Lemmens, filed for a judicial review that not only led to Health Canada providing clinical trial data relating to several drugs and but also helped lead to the regulator's decision to begin proactively releasing CSRs related to regulatory decisions.^{139,141} Notably, Health Canada chose not to appeal the legal decision in the Doshi case and instead took the opposite course of beginning to proactively release CSRs. This may highlight that Health Canada was not fully aligned with industry and in part had an interest in enhancing transparency, and the judicial review shifted its interests toward pursuing greater transparency of CSRs. These examples illustrate the potentially important role of transparency research and advocacy for increasing clinical trial transparency.

6.2 Dynamics of changing policy and practices relating to trial transparency

While strategic interests and power give rise to actions and omissions which shape the policy context and have resulted in partial transparency (as described above), changes to the policy context may in turn shift strategic interests and power. The role of the AllTrials campaign in helping to influence the reporting practices of public clinical trial sponsors in the UK illustrates this dynamic process. AllTrials supplied data to the House of Commons Science and Technology Select Committee which demonstrated that in January 2019 only 48.1% of trials sponsored by UK universities and NHS trusts had reported results in EUCTR within one year of trial completion.¹⁹⁷ After the committee notified these public trial sponsors that they could called to

account if they did not make progress in reporting results, the rate of reporting increased to 63.9% by October 2019. Although other factors may have played a role, public scrutiny of reporting practices was associated with an increase in reporting.¹⁹⁷ In effect, the monitoring and public accountability for reporting practices faced by UK research institutions shifted their strategic interests toward focusing on reputational risk and diminished their power to ignore the poor record of reporting by investigators at their institutions.

The strategic interests and power relations outlined in this chapter suggest that moving toward greater transparency must involve more than highlighting the problem of nonpublication or even describing policies that could address this problem. Rather, it is likely important to influence the strategic interests and power of relevant actors, and to implement a mechanism of accountability. Progress toward greater transparency is not inevitable, and transparency policies in some cases have been reversed. A CIHR policy that grant recipients must publish their results within 12 months of trial completion was retracted three months after it was posted online in December 2010, which may have been due to influence from industry sponsors.⁸⁷ This reversal a decade ago may have reflected how CIHR's interests in pursuing good science and in aligning itself with industry pulled the agency in different directions. (CIHR's more recent 2020 commitment to develop policy guidance that would require results reporting within a 12-month timeframe is promising, but how it plays out remains to be seen.)¹⁶⁶ The EMA's decision to release trial information about two anti-obesity drugs to the Nordic Cochrane centre following an investigation by the European Ombudsman may also illustrate the importance of strategic interests.¹³⁷ The EMA repeatedly argued that it could not release CSRs due to the need to protect commercial interests, which reflected the regulator's alignment with industry.¹³⁶ After the European Ombudsman stated that the EMA had committed maladministration and recommended

that documents be shared, it is notable that the EMA did not have to comply, because the ombudsman's recommendations are not binding.¹⁹⁸ However, it was no longer in the strategic interest of the EMA to deny the application for CSRs, because not complying with the ombudsman's recommendation would undermine the reputation of the regulator. The ombudsman's inquiry and the publicity regarding the ombudsman's finding of maladministration brought the EMA publicly to account and undermined the power the EMA to adhere to its previous position. These shifts in strategic interests, power, and accountability may also help explain why the EMA ultimately went further than the ombudsman's recommendation and started proactively releasing CSRs.^{135,138}

6.3 Ethical implications

This study has suggested that reciprocity between trial participants and researcher involves an ethical obligation to report research results, but that this reciprocity is weakened by a lack of accountability of researchers to trial participants or even to ethics boards regarding trial reporting. Some trial investigators expressed a sense of duty toward trial participants to reporting their findings, reflecting an individual responsibility to be transparent in clinical research. However, this analysis highlights that their activities take place within the broader research system. The responsibility to report trial findings does not lie with trial investigators alone. They may have greater control over reporting in investigator-initiated trials than in sponsored trials. On another level, it may be understandable if they make choices which they believe will sustain their ability to continue with their research programs, even if it means that some trials go unpublished. Similarly, REBs have a responsibility to ensure ethical principles are respected in clinical research, but they may face constraints such as their capacity to monitor trial reporting

within their budgets. This analysis has also highlighted that actors within the clinical trial reporting system have varying levels of power to influence reporting and one another. As it is reasonable that we only have responsibility over matters under our control, it follows that power confers greater responsibility to bring about transparency of clinical trial reporting. Canadian trial investigators have a responsibility to report research results, but an even greater responsibility may rest with industry sponsors, Health Canada, CIHR, and research institutions. They have greater power to influence clinical trial reporting and therefore greater responsibility to ensure it is carried out to honour the contributions and consent of trial participants.

6.4 Transparency of individual patient data and clinical study reports

Although the increasing availability of individual patient data and CSRs has contributed to transparency of clinical trials, the transparency of these forms of clinical trial information is still incomplete. The ICMJE requires data sharing statements to be included with submissions to journals but does not actually require that individual patient data be shared as a condition of publication.⁸⁰ An audit of pharmaceutical company transparency policies on clinical trial information found that most of the top companies globally by expenditure have policies on individual patient data sharing, but that often their transparency policies are ambiguous and do not cover all trials.¹⁶⁰ A review of transparency policies of leading noncommercial funders globally by expenditure found that only a minority required individual patient data sharing.¹⁷⁰ Regulators in Canada and the EU release CSRs both proactively and by request.^{135,139} However, this does not provide full transparency of trials, because regulators may not have data on all clinical trials¹²¹ and disclosure policies do not appear to cover all clinical trials. The EU policy does not cover clinical data not held by the EMA, such as “clinical trials on an authorised

product conducted by independent investigators and not submitted to the [EMA].”¹⁹⁹ Health Canada’s policy indicates CSRs are only available following a regulatory decision, which could lead to delays and omissions of clinical trial information that is made available.¹³⁹ For example, trials of drugs for which no application for market approval has been made might provide valuable information to the scientific community but would appear to be excluded from Health Canada’s disclosure policy.

A consideration of strategic interests and power may be useful to understanding not only transparency in reporting of trials in journals and trial registries but also transparency of other forms of clinical trial information, such as individual patient data and CSRs. Industry sponsors have a commercial interest in controlling how data about their products are reported, and may also hesitate to share clinical trial information that could be used by their competitors.¹⁸⁸ Trial investigators have career-related incentives to avoid sharing data, because retaining data may protect their ability to publish secondary analyses, which could help with career advancement or obtaining funding.¹⁸⁸ Similarly, research institutions may not provide infrastructure for data sharing or reward this activity, because data sharing may not attract funding to the university. As discussed above, Health Canada previously treated clinical trial data from companies as commercially confidential and proprietary, but adopted a policy of release CSRs on request and proactively following a judicial review which undermined its earlier position.^{139,141} The judicial review sought by Peter Doshi to obtain clinical trial information helped lead to this change in policy at Health Canada and has increased transparency, but there is still not full transparency of individual patient data and CSRs in Canada.

6.5 Summary

As described in this chapter, the challenges of moving toward full transparency of clinical trial reporting may be understood through the strategic interests and power of various actors which give rise to their actions and omissions, leading to partial transparency of clinical trial results. The strategic interests and power of actors within the clinical trial reporting have been explored through the following themes: balancing transparency with strategic interests, the influence of dominant stakeholders on policy making, ethical obligations without accountability, and advocacy for trial transparency. This analysis has emphasized the importance of strategic interests and power in limiting transparency with the implication that actors with greater power have a greater responsibility for acting to improve transparency.

Chapter 7: Discussion and conclusions

Clinical trials are only selectively reported, leading to misrepresentation of medical research in the published literature.¹⁻³ Consequently, clinicians may have to rely on partial information when making treatment decisions, patients may be exposed to excessive risk due less informed care and duplicative research, and funding may be wasted on research which does not contribute to general knowledge.^{17,18,54}

As stated in the opening chapter, the primary objectives of this study were (i) to understand whether and how industry sponsors of clinical trials influence decisions to report trial results, (ii) to understand factors contributing to nonpublication and publication bias in clinical trials, and (iii) to understand how the experiences and views of trial participants, trial investigators, and others relate to whether researchers have a duty to trial participants to report research findings. A secondary objective was (iv) to identify implications of the study's findings for policy to address nonpublication and publication bias in clinical trial research.

This concluding chapter serves several purposes. First, it summarizes key findings and contributions from the study relating to industry influence in clinical trial reporting, factors that may influence nonpublication and publication bias, clinical trial reporting as an ethical responsibility to trial participants, and clinical trial transparency in the context of strategic interests and power. Second, it provides a description of overall implications of the study's findings for policy on clinical trial reporting, when the findings from all components of the study are taken as a whole. Third, it describes the strengths and limitations the study. Fourth, it highlights directions for future research on clinical trial reporting. Fifth, a final section states the study's conclusions.

7.1 Summary of key findings and contributions

This section summarizes this study's key findings and contributions on the topics of industry influence in clinical trial reporting, factors relating to nonpublication and publication bias in clinical trials, reporting clinical trial findings as an ethical responsibility to research participants, and clinical trial transparency in the context of strategic interests and power. (For a tabular summary of key contributions of this study, see **Table 4**.)

Industry sponsor influence in clinical trial reporting

Industry sponsors have a weaker incentive to report the results of certain trials, including those with unfavourable results and those for drugs they have decided not to market. Interviews with trial investigators and others highlighted mechanisms through which sponsors may influence whether a trial is reported. First, sponsors may influence reporting by stopping a trial early for business or strategic reasons and not proceeding to publish the findings. Second, sponsors typically own and may control access to the key data from a trial, which may be an obstacle to investigators reporting trial results if the sponsor does not support publication. Third, sponsors may negotiate clinical trial agreements in multicentre trials which do not protect the ability of site investigators to publish based on all of the data from a trial if the sponsors and trial leaders do not proceed with publication. Early phase internal company trials of investigational drugs are an additional source of unpublished trials. Importantly, dependence of research programs on industry sponsors may weaken the ability of investigators to report trial results.

This study makes various contributions to understanding industry influence in clinical trial reporting. While investigator surveys have indicated trials may be stopped by sponsors for business reasons,^{29,30,33,72-75} our study highlighted that when sponsors stop trials prematurely this

may be associated with nonpublication. We also found that small biotech firms faced with negative trial results may close their operations without completing ongoing trials or reporting their results. Concerns about sponsor ownership and control of trial data are not new but have largely focused on the need for independent analysis,^{69,76-79} whereas our findings highlight that lack of access to data may also hinder an investigator's ability to report findings. Medical school surveys have indicated clinical trial agreements typically did not allow sponsors to decide whether a trial is published and often allowed site investigators to publish based on local site data,^{81,83} while our study highlights that the ability to publish site data only weakly protects the right to publish because such analyses are unlikely to allow for inferences about a study's primary outcomes. In addition, our study is consistent with previous articles suggesting nonindustry funders often provide funding that is inadequate for conducting a trial,^{89,90} while adding that this may contribute to dependency of clinical research programs on industry sponsors.

Factors contributing to nonpublication and publication bias

While a range of factors contribute to nonpublication and publication bias, our study suggests powerful incentives within the research system, which provide greater rewards for reporting positive findings than negative findings, shape clinical trial reporting practices. Investigator experiences or perceptions of the difficulty of publishing negative findings in journals may play a role. The accounts of interview participants suggested positive findings may be more likely to lead to industry and nonindustry funding for trial research. Research institutions may contribute to incentives of researchers to focus on positive findings through hiring and promotion decisions which reward researchers for attracting funding and publishing in high-impact-factor journals.

Policies to encourage full reporting of clinical trials have not been strong enough to counterbalance these incentives. CIHR has not previously required reporting of trial results within a specific timeframe, while Health Canada has not introduced mandatory requirements for investigators or sponsors to report trial findings.

This study builds on previous research regarding factors contributing to nonpublication and publication bias. Surveys of investigators highlight that unpublished trials have often not been submitted for publication and that this is related to factors such as lack of time and low priority.^{14,35} Our study helps clarify that investigator decisions on whether to submit trials are influenced by strong incentives related to career advancement and recognition. While providing empirical support to previous critiques of incentives within medical research,^{46-48,110,113,200} our study makes additional contributions to understanding selective publication. Interview participant accounts suggested positive trials were more likely to lead to funding from not only granting agencies but also pharmaceutical companies, who might wish to develop a promising drug further. Research institutions might reinforce emphasis on positive trial findings not only through hiring and promotion but also in communications such as institutional newsletters which celebrate potential medical advances. In addition, research institutions tended to lack well-established programs to support investigators to report in registries or journals.

Clinical trial reporting as a responsibility to trial participants

Interviews with trial participants, investigators and others suggested that when individuals choose to participate in a clinical trial, there is often an implicit understanding between researchers and participants involving a responsibility to report results. Accounts of trial participants and investigators suggested clinical trials involved reciprocity. Trial participants

contributed their time and exposed themselves to risk with the expectation that clinical trials would advance medical knowledge. Typically, they were motivated to join a trial at least in part due to a desire to help others and believed reporting trial results was important. Comments from trial investigators suggested reporting trial findings is an important part of respecting the contributions of trial participants and honouring informed consent.

This study complements previous research and commentary on the views of trial participants and ethical dimensions of clinical trial reporting. While previous studies have highlighted altruistic motivations for participating in trials,³⁶⁻³⁹ our study adds that even when individuals are strongly motivated to join a trial to access treatment this may be accompanied by a desire to help others with similar health problems. A previous study found that patients surveyed typically believed that publicly reporting clinical trial results was important.¹¹⁸ Our study found that most individuals who had recently participated in a trial felt that reporting trial results was important, and it suggested trial participants may understand trials as part of a reciprocal relationship involving an expectation that research will contribute to knowledge. In addition, this study provides empirical support for arguments that when results are not published, researchers break an implicit agreement with participants and undermine informed consent.^{19,41-43}

Clinical trial transparency in the context of strategic interests and power

The challenges of moving toward full transparency of clinical trial reporting may be understood through the strategic interests and power of various actors which give rise to their actions and omissions, leading to only partial transparency. Industry sponsors, research institutions, journals, and clinical trial investigators balance their interests in transparency with their other strategic interests either as organizations or individuals. Health Canada and CIHR are

well-positioned to make policies to increase transparency of clinical trial reporting, but may be influenced by industry sponsors and research institutions as dominant stakeholders. Trial participants have a strong moral claim to call for greater transparency and REBs have a role to ensure transparency, but the ethical obligations to report trial results are not supported by effective accountability mechanisms. Although strategic interests have contributed to limiting transparency, it may be possible to move toward full transparency through research and advocacy that shifts strategic interests and the relative power of different actors. Industry sponsors, Health Canada, CIHR, and research institutions have greater power and therefore greater responsibility to increase trial transparency.

A previous commentary on reducing waste at various stages of biomedical research considered the interests and interrelated actions of a range of actors.⁴⁷ It highlighted that “the status quo in biomedical research is based on the complex and interdependent actions of diverse actors, each operating within their own systems of risks and incentives.”⁴⁷ The analysis of transparency presented in the preceding chapter considers a broader range of actors, and it identifies not only incentives but also the relative power of the actors involved. A recent book chapter on transparency and pharmaceutical policy highlights the importance of understanding transparency through power relations and how relationships involving transparency may be characterized by conditions stipulating what information must be disclosed by which actors and to whom.²⁰¹ Our study has focused in part on the responsibility of pharmaceutical companies and trial investigators to publicly disclose the results of clinical trials in journal articles and trial registries, while also providing a discussion of regulatory policies to publicly disclose clinical trial information collected from companies. We have related clinical trial transparency to the strategic interests and power of a range of actors, including not only industry sponsors, trial

investigators, and regulators but also journals, research institutions, trial participants, REBs, and transparency researchers and advocates. Consistent with the book chapter's emphasis on power relations, our analysis outlines how strategic interests and power may constrain the degree of transparency of clinical trial research, although transparency gains have been made and further gains are possible.

7.2 Policy implications

Regulatory policy

Regulatory requirements to report clinical trial results represent a fundamental policy for moving toward better clinical trial reporting practices. Experience in the US and EU suggests monitoring and enforcement may be important for bringing about higher overall compliance with requirements.^{44,45} In the spring of 2021, the FDA issued its first notice of noncompliance to a trial sponsor and suggested it would pursue enforcement actions against others with unreported trials.¹⁵¹⁻¹⁵³ The EU has previously lacked penalties for noncompliance, but member states will be required to introduce enforcement measures when the EU Clinical Trials Regulation comes fully into force.^{149,150} These reporting requirements could be improved by the inclusion of phase 1 trials, which are excluded from mandatory reporting in the US and largely excluded in the EU.^{44,45} As Canada lacks similar regulatory policy, one of the principal actions Health Canada could take to address unreported clinical trials would be to adopt regulatory requirements for clinical trial reporting, accompanied by monitoring and enforcement measures. In addition, Health Canada should consider whether regulatory policy is needed to address the practice of industry sponsors prematurely stopping trials for business or strategic reasons. This practice is a

source of unreported trials and undermines the social benefit and ethical basis for conducting a trial.¹⁸³⁻¹⁸⁵

Research institutions and research ethics boards

Research institutions and REBs could address nonpublication and publication bias in various ways. Universities and other research institutions could help incentivize full reporting of trials by ensuring assessment of researchers takes into account whether research findings have been fully reported^{17,46-48,148} and by providing academic credit for reporting in trial registries.¹⁶⁵ Research institutions are also in a position to monitor and support investigators to report research findings in trial registries, which could include collecting trial registration information, providing reminders to report, and offering training and other types of support to investigators.^{173,174,189} As REBs already collect information about clinical studies, they could assist with implementation of such programs.^{173,174} It would also be valuable for research institutions or REBs to conduct periodic audit of clinical trial reporting and publicly report the results,¹⁷² although REBs might lack the capacity to fulfill this role without changes to their responsibilities and budgets. Importantly, our study also highlighted that research institutions may need to take action to ensure investigators are able to report results based on all data in industry-sponsored, multicentre trials in cases where the sponsor and trial leaders have not proceeded with timely publication. This might involve adopting policy to require language be included in clinical trial agreements to protect the right to publish based on all data from a trial in such circumstances. As individual research institutions may be apprehensive to take action, Health Canada could consider taking regulatory action to address this issue.

Funding-related policies

Nonindustry funders are also in a position to influence clinical trial reporting practices.¹⁷⁰ First, funders may have an influence through mandatory reporting requirements. Although CIHR has not previously specified a timeline during which grant recipients must report trial results, the agency has stated it would adopt policy guidance in 2021 to require trial results to be reported within a “12-month timeframe.”¹⁶⁶ If monitored and enforced, this could help encourage reporting among grant recipients. Monitoring and enforcement are as yet unclear, but CIHR stated that penalties for noncompliance were under discussion. Second, peer review policies which set out how grant recipients should be assessed are an important area where funders may influence trial reporting.⁴⁷ CIHR has stated it will require applicants to provide the reporting status of their previous clinical trials when applying for funding,¹⁶⁶ which could encourage applicants to report trial findings. As noted above, the DORA declaration recommends funding agencies should “clearly highlight . . . that the scientific content of a paper is much more important than publication metrics or the identity of the journal in which it was published.”¹⁶⁷ CIHR could more consistently communicate this approach in materials provided for peer review of applications for funding to conduct clinical trials.¹⁶⁹ This could help encourage investigators to report high-quality research regardless of study outcome, rather than focusing their efforts on publishing novel results in high-impact-factor journals. More broadly, the research system is characterized by dependence on industry sponsors to fund a large part of clinical trial research.²² Providing greater public investment in independent research could help address this dependence by increasing the share of research which is not subject to commercial incentives to selectively report clinical trial findings.

7.3 Importance of reporting results in academic journals and trial registries

While this study has focused primarily on the reporting of trial results in journals and trial registries, sharing of individual patient data and release of CSRs have emerged as additional important forms of clinical trial transparency. These various forms of information about clinical trials should be viewed as providing complementary information about trials rather than as substitutes for one another. Journal publications allow scientists to provide trial results to the scientific community and benefit from the process of peer review. Clinical trial registries provide a means to report information about the design and results of a trial in a structured manner, which is also an efficient way to report results which may not be of interest to many journals. Provision of individual patient data permits the re-analysis of data from a trial to verify the results, perform meta-analyses with pooled data, and conduct secondary analyses.¹⁶⁰ CSRs provide comprehensive information about a trial, which allows for re-analysis and may reveal information about a trial that would not be apparent in other sources of clinical trial information.¹²¹

We have not reached a stage where individual patient data and CSRs are fully available (as described in Chapter 6). Although individual patient data and CSRs promise to provide greater transparency, reporting of trial results in journal articles and trial registries will continue to be highly important. Reporting results in journals and registries provide information on trial outcomes that is accessible and may be made promptly available.²⁰² Reporting of clinical trial results within trial registries is of particular importance, because it is efficient to report results within registries, reporting within registries may be easily monitored, changes to study design may be detected in registries, and clinical trial information tends to be more complete in registries than in journal articles.²⁰³ Access to individual patient data and CSRs provide

additional value. However, they require additional investment of effort and resources to process, and most people lack the time and resources to review CSRs or re-analyze individual patient data. Due to the value provided by reporting results in journals and registries, it is still worthwhile to pursue full reporting of trials in journals and registries even while aiming to enhance transparency by expanding access to individual patient data and CSRs.²⁰²

7.4 Strengths and limitations of the study

The use of a qualitative research design involving semistructured interviews and an iterative process of conducting interviews and analysis was a strength of this study. This approach allowed for an open-ended exploration of participant experiences connected to trial research, such as discussing specific unpublished trials and an investigator's reflections on factors related to nonpublication. When asking about the value of reporting research results or other topics, it was possible to explore nuances of views. As new issues arose during this study, these could be analyzed between interviews and raised in future interviews to build toward a greater understanding of key concerns regarding clinical trial reporting.

Another strength of the study was the inclusion of a diverse sample of participants. The study included participants from 3 provinces, which was important as experiences and views might differ due to differences in population, health policy, or clinical trial infrastructure across provinces. All trial investigators who participated had experience conducting both trials funded by industry and trials funded by nonindustry sources, and investigators specialized in a range of medical disciplines. Similarly, trial participants had taken part in trials investigating treatments for a variety of health conditions. Overall, interviews with trial participants, trial investigators, and others involved in the conduct, administration or ethical review of trials provided a rich

collection of data offering insights into the process of trial reporting and views regarding reporting practices and ethics.

The study also had various limitations. Interviews did not include representatives of pharmaceutical companies, noncommercial funders, medical journals or regulators. These types of participants might have offered insights regarding factors contributing to nonpublication and policy to address nonpublication. Trial participants had taken part in trials related to several health conditions, but did not include those who had participated in some common types of trials such as trials of cancer treatments. As our study included only participants in Canada, it is unclear how generalizable our findings are outside of Canada due to differences in funding, policy, and health care systems. Among trial investigators, administrators and REB members invited to take part in this study, a high proportion either declined to participate or did not respond. It is possible that those who volunteered to take part in an interview differed from those that did not, such as holding different views toward the value of reporting trial findings.

7.5 Future research

Our analysis of industry influence on clinical trial reporting found that small biotech firms faced with negative results may close as a company without completing ongoing trials, publishing their findings, or sharing data with investigators to enable them to report on a trial. It may be valuable to conduct further research to better understand how this occurs and how often it occurs, which might help identify ways to address this type of premature stopping of trials and nonpublication.

Policy evaluation in the area of clinical trial reporting represents an important area of future research. At the level of regulatory policy, EU member states will be required to adopt penalties

for noncompliance with regulatory requirements to report clinical trials, but penalties and enforcement may vary across countries and may differ from measures in the US.^{149,153} This may provide an opportunity to evaluate the impact of different regulatory approaches. At the level of research institutions, our study highlighted that it would be valuable for institutions to establish programs to monitor and support investigators to report findings in trial registries.^{173,174,189} Researchers might collaborate with research institutions to design and evaluate pilot phases or full implementation of such programs. At the level of funding policy, CIHR's planned adoption of a requirement that grant recipients report clinical trial results within a specific timeframe could be evaluated after the policy is implemented.¹⁶⁶

As interviews for this study included only participants in Canada, future research could investigate industry influence and other factors that may contribute to nonpublication and publication bias in other countries. This might identify variation across countries or provide additional insights into factors highlighted in this study and policy responses.

7.6 Conclusions

Industry sponsors may influence whether clinical trials are reported through stopping trials early and not reporting results, ownership and control of data, clinical trial agreements which do not fully protect an investigator's right to publish, control of internal company trials, and funding dependency. While companies have a commercial incentive to selectively report clinical trials, other powerful incentives within clinical research also appear to favour publication of positive over negative trials. Positive findings are perceived to be easier to publish, to help investigator's ability to access industry and nonindustry research funding, and to be rewarded by research institutions in hiring, promotion and recognition.

The value of clinical trial reporting was recognized by trial participants, investigators, and others involved to clinical trial research who participated in this study. Most participants in trials were motivated to join a trial in part to help others. Interviews suggested that when participants enter a trial, there is often an implicit understanding between researchers and participants involving a responsibility to report results. In effect, clinical trial reporting is a necessary part of informed consent. Nonetheless, obstacles to full reporting of clinical trials are many and policy on various levels is required to help ensure trials are reported regardless of the strength and direction of the findings.

Nonpublication and publication bias may be understood through the strategic interests and power of influential actors that give rise to actions and omissions limiting the transparency of clinical trial reporting. Trial participants have a strong moral claim to call for greater transparency and REBs have role to ensure transparency, but the ethical responsibility to report trial results is not supported by effective accountability mechanisms. Transparency researchers and advocates may have an important role to play in prompting other actors to take steps toward greater transparency of clinical trial reporting.

Research institutions could take action to protect the right of investigators to publish when they are involved in industry-sponsored research and to reward researchers for good clinical trial reporting practices. REBs and research institutions could monitor trial reporting, support researchers to report results in registries, and conduct annual audits of clinical trial reporting. CIHR has taken steps toward strengthening its policies on clinical trial reporting. It will be important for the agency to ensure it implements reporting requirements with penalties for noncompliance. Health Canada could not only introduce mandatory clinical trial reporting but also consider whether regulatory actions are needed to address premature stopping of trials for

commercial reasons and to protect the right of site investigators to report the results of industry-sponsored trials when sponsors and trial leaders do not proceed with timely reporting. The federal government and CIHR could consider providing greater support for independent clinical trial research, which is not subject to commercial incentives for selective reporting.

In summary, selective reporting of clinical trials arises for a variety of reasons. This study has highlighted the problem of unpublished clinical trial research in Canada, including key contributory factors. If the results of trial research are not reported, patient care may suffer. Policy to promote full reporting of trials may be strengthened by recognizing the factors that contribute to nonpublication and publication bias.

Table 1. Types of interview participants and inclusion criteria

Participant type	Inclusion criteria	Rationale
Clinical trial investigator	Conducted ≥ 1 clinical drug trial	Will have experience relevant to trial reporting
Clinical research coordinator	Coordinated ≥ 1 clinical drug trial	May have experience relevant to clinical trial reporting
Clinical REB member	≥ 1 year of experience as clinical REB member	Experience in ethical review and familiarity with practice and policy relating to clinical trial reporting
Research administrator	Knowledge of policy and practice related to dissemination of clinical trial findings and/or relations with trial sponsors	Contribute experience, knowledge and views from policy or administrative perspective
Past trial participant	Participated in ≥ 1 clinical drug trial while at least 18 years of age; participation in the 5 years prior to interview, but has now ended	Will have experience related to trial participation and trial reporting

REB=research ethics board

Table 2. Interview participant characteristics

a. Trialists

Characteristic*	Trialists (n=17)
Primary appointment	
University or academic teaching hospital	10
Other (e.g., private practice, cancer centre)	7
Experience in role	
≤5 years	0
>5 years	17
Province	
Alberta	0
British Columbia	9
Ontario	8
Types of funding	
Nonindustry only	0
Industry only	0
Both industry and nonindustry	17
Most senior role	
Principal Investigator for site	3
Principal Investigator for trial	14
Trial type	
Single site only	0
Multiple site only	1
Both single and multiple site	16

*Classifications were based on those used for an investigator survey by Rochon et al (2011).⁸²

b. Research administrators, research ethics board members and clinical research coordinators

Characteristic	Research administrators (n=3)	REB members (n=3)	Research coordinators (n=1)
Primary appointment			
University or academic teaching hospital	3	1	0
Other (e.g., private practice, cancer centre)	0	2	1
Experience in role			
≤5 years	0	1	0
>5 years	3	2	1
Province			
Alberta	1	1	0
British Columbia	0	2	1
Ontario	2	0	0

Research coordinator=clinical research coordinator REB=research ethics board

(continued on next page)

Table 2. Interview participant characteristics (continued)

c. Past trial participants

Characteristic	Past trial participants (n=10)
Sex	
Female	7
Male	3
Age	
≤65 years	5
>65 years	5
Education, highest level completed	
Elementary	1
Secondary	3
Community college	1
University	5
Province	
Alberta	3
British Columbia	7

Table 3. Interests, power, and actions and omissions of actors connected to clinical trial research

Actor	Strategic interests	Power to influence	Actions and omissions
Industry sponsors	<ul style="list-style-type: none"> -Develop marketable products -Commercial interest in selectively reporting favourable results -Manage reputational risk 	<ul style="list-style-type: none"> -Influence investigators and research institutions through funding dependency -Economic power and prestige may allow influence on Health Canada and CIHR 	<ul style="list-style-type: none"> -Influence reporting decisions by stopping trials early and not reporting results, owning and controlling data, negotiating clinical trial agreements that do not fully protect right to publish, and nonreporting of internal trials -May influence Health Canada and CIHR policy
Trial investigators	<ul style="list-style-type: none"> -Advance medical knowledge -Career-related incentives to attract funding from industry and nonindustry sources, and publish in prestigious journals 	<ul style="list-style-type: none"> -Exercise some control over reporting, especially in investigator-initiated research -May be influenced by career-related incentives and industry sponsor influence 	<ul style="list-style-type: none"> -Do not report all trials and preferentially submit trials with positive findings for publication
Journals and reviewers	<ul style="list-style-type: none"> -Publish high-quality research -May aim to publish novel and significant findings to raise journal impact factor to build prestige or increase revenue 	<ul style="list-style-type: none"> -Gatekeeping role in academic publishing, which could be used to either emphasize quality or novelty and statistical significance 	<ul style="list-style-type: none"> -Reviewers appear to favour clinical trials with positive findings, which may discourage investigators from submitting negative findings
Research institutions	<ul style="list-style-type: none"> -Facilitate disinterested pursuit knowledge and free exchange of information -Attract funding from industry and nonindustry sources -Manage reputational risk 	<ul style="list-style-type: none"> -Ability to influence researcher behaviour through promotion, bonuses, recognition -Some bargaining power with industry from providing expertise, credibility, and access to patients, but may be weakened by competition for funding 	<ul style="list-style-type: none"> -Reward researchers who attract funding and publish in prestigious journals, which may incentivize publication bias -Allow clinical trial agreements that may not fully protect right to publish -May lack effective programs to help ensure trials are reported
Canadian Institutes of Health Research	<ul style="list-style-type: none"> -Mandate to fund production and dissemination of research -Aligned with research institutions and industry 	<ul style="list-style-type: none"> -As national funder of research, agency could influence clinical trial reporting through policies on reporting and peer review of grants 	<ul style="list-style-type: none"> -History of weak policies, such as lack of timeline for results reporting -Announced it will introduce timelines for reporting and require grant recipients to provide reporting status of past trials

(continued on next page)

Table 3. Interests, power, and actions and omissions of actors connected to clinical trial research (continued)

Actor	Strategic interests	Power to influence	Actions and omissions
Health Canada	<ul style="list-style-type: none"> -Enhancing transparency might increase legitimacy with public -Actions suggest aligned with industry (e.g., treating clinical trial data as confidential until recently) 	<ul style="list-style-type: none"> -Could influence behaviour of researchers, research institutions, and industry sponsors through regulation -Subject to oversight from government of the day and industry influence 	<ul style="list-style-type: none"> -Releases SBDs and has started releasing CSRs following regulatory decisions -Unlike regulators in US and EU, Health Canada has yet to adopt regulatory requirements to report trials in trial registries
Trial participants	<ul style="list-style-type: none"> -Advance medical knowledge -Access treatment, free drugs or medical supplies, and better care -Help health provider or researchers 	<ul style="list-style-type: none"> -Potential power as trials depend on participants; also, researchers feel duty to participants to report, but reciprocity may be weakened because participants do not find out if results are reported 	<ul style="list-style-type: none"> -Do not typically seek assurances or confirmation that results are reported, or collectively advocate for reporting
Research ethics boards	<ul style="list-style-type: none"> -Role to uphold ethical principles -Interests may also reflect those of researchers and research institutions they are affiliated with or, in the case of for-profit REBs, industry sponsors 	<ul style="list-style-type: none"> -Authority of ethics approval provides some power over sponsors and researchers -Power may be limited by relationship with affiliated research institutions or, if for-profit, industry sponsors 	<ul style="list-style-type: none"> -Interpret role as protecting individual patients rather than safeguarding reporting practices -Tend not to play an active role in monitoring clinical trial reporting or ensuring trials are reported
Transparency researchers and advocates	<ul style="list-style-type: none"> -Access to clinical trial information to inform meta-analyses and clinical decision-making -Protect public health 	<ul style="list-style-type: none"> -Derives some power to influence by bringing scrutiny and publicity to nonreporting 	<ul style="list-style-type: none"> -TrialsTracker tool developed by academics at Oxford highlighted poor record of trial results reporting at some Canadian research institutions

CIHR=Canadian Institutes of Health Research CSR=clinical study report EU=European Union REB=research ethics board SBD=Summary Basis of Decision information US=United States

Table 4. Summary of key contributions of this study

Topic	What is already known on this topic	What this study adds
Industry sponsor influence in clinical trial reporting	<ul style="list-style-type: none"> • Many clinical trials and other biomedical studies are either not published as journal articles or only published after a long delay.¹⁻³ • Although the US and the EU require reporting of applicable clinical trials within trial registries, studies have found low compliance with these reporting requirements.^{44,45} • In some cases, internal documents of pharmaceutical companies have revealed the intention to suppress unfavourable results.^{26,27,175} 	<ul style="list-style-type: none"> • Industry sponsors may influence the decision on whether to report clinical trials in various ways, which include owning and controlling access to data. • Clinical trial agreements may fail to protect the ability of site investigators to publish results based on all data from a trial when sponsors and trial leaders do not proceed with timely publication. • Sources of unpublished clinical trials include early phase internal company trials and trials of small biotech firms that cease operations without publishing their results.
Factors relating to nonpublication and publication bias in clinical trials	<ul style="list-style-type: none"> • Many clinical trials are not published and positive trials are more likely to be published than negative trials.¹⁻³ • The majority of unpublished medical and health-related studies have not been submitted for publication.³⁵ • Academic criteria for hiring and promotion often include the number of articles published and publication in journals with a high impact factor.^{48,110} 	<ul style="list-style-type: none"> • Reporting practices are shaped by incentives within the research system which favour publication of positive over negative trials • Trial investigators more strongly associated positive clinical trials than negative trials with funding opportunities, academic promotion, bonuses, and recognition. • Research institutions tended to lack well-resourced, proactive policies and practices to ensure trial findings are reported in registries or journals.
Reporting clinical trial findings as an ethical responsibility to research participants	<ul style="list-style-type: none"> • Clinical trial participants tend to be motivated to participate in trials in part for altruistic reasons.³⁶⁻³⁹ • A survey of patients found that most believed it was important to make clinical trial results publicly available.¹¹⁸ • The principle of respect for persons involves respecting the autonomy of research participants, who must be informed of risks and benefits of research as part of the basis of informed consent.^{119,120} 	<ul style="list-style-type: none"> • Even individuals primarily motivated to participate in a trial to access treatment may wish to help other patients out of a sense of solidarity. • Trial participants felt reporting results was important and may understand trials as part of a reciprocal relationship involving an expectation trials will contribute to knowledge. • Accounts of trialists suggest reporting results is part of reciprocity with trial participants and is a necessary part of honouring informed consent.

(continued on next page)

Table 4. Summary of key contributions of this study (continued)

Topic	What is already known on this topic	What this study adds
Clinical trial transparency in the context of strategic interests and power	<ul style="list-style-type: none"> • Transparency of clinical trial reporting is incomplete.^{1-3,44,45} • Industry sponsors, nonindustry funders, regulators, research institutions, and trial investigators act according to their own risks and incentives.⁴⁷ 	<ul style="list-style-type: none"> • The strategic interests and power of industry sponsors, research institutions, and others connected to trial research give rise to their actions and omissions, leading to partial transparency of trial research. • Trial participants have a strong moral claim to call for greater transparency and REBs have role to ensure transparency, but the ethical duty to report trial results is not supported by effective accountability mechanisms. • Industry sponsors, Health Canada, CIHR, and research institutions have greater power than other actors and therefore greater responsibility to increase trial transparency.

CIHR=Canadian Institutes of Health Research REB=research ethics board

References

1. Canestaro WJ, Hendrix N, Bansal A, Sullivan SD, Devine EB, Carlson JJ. Favorable and publicly funded studies are more likely to be published: a systematic review and meta-analysis. *J Clin Epidemiol.* 2017;92:58-68.
2. Scherer RW, Meerpohl JJ, Pfeifer N, Schmucker C, Schwarzer G, von Elm E. Full publication of results initially presented in abstracts. *Cochrane Database Syst Rev.* 2018;11:MR000005.
3. Schmucker C, Schell LK, Portalupi S, et al. Extent of non-publication in cohorts of studies approved by research ethics committees or included in trial registries. *PLoS One.* 2014;9(12):e114023.
4. Dickersin K, Chan S, Chalmers TC, Sacks HS, Smith H, Jr. Publication bias and clinical trials. *Control Clin Trials.* 1987;8(4):343-353.
5. Hemminki E. Study of information submitted by drug companies to licensing authorities. *British medical journal.* 1980;280(6217):833-836.
6. Simes RJ. Publication bias: The case for an international registry of clinical trials. *Journal of Clinical Oncology.* 1986;4(10):1529-1541.
7. Kho ME, Brouwers MC. Conference abstracts of a new oncology drug do not always lead to full publication: proceed with caution. *J Clin Epidemiol.* 2009;62(7):752-758.
8. Lensen S, Jordan V, Showell M, et al. Non-publication and publication bias in reproductive medicine: a cohort analysis. *Hum Reprod.* 2017;32(8):1658-1666.
9. Sanossian N, Ohanian AG, Saver JL, Kim LI, Ovbiagele B. Frequency and determinants of nonpublication of research in the stroke literature. *Stroke.* 2006;37(10):2588-2592.

10. Shamliyan T, Kane RL. Clinical research involving children: registration, completeness, and publication. *Pediatrics*. 2012;129(5):e1291-1300.
11. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet*. 2004;363(9418):1341-1345.
12. Hopewell S, Clarke M, Stewart L, Tierney J. Time to publication for results of clinical trials. *Cochrane Database Syst Rev*. 2007(2):MR000011.
13. Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev*. 2009(1):MR000006.
14. Scherer RW, Ugarte-Gil C, Schmucker C, Meerpohl JJ. Authors report lack of time as main reason for unpublished research presented at biomedical conferences: a systematic review. *J Clin Epidemiol*. 2015;68(7):803-810.
15. Song F, Parekh-Bhurke S, Hooper L, et al. Extent of publication bias in different categories of research cohorts: a meta-analysis of empirical studies. *BMC Med Res Methodol*. 2009;9:79.
16. Chalmers TC, Frank CS, Reitman D. Minimizing the three stages of publication bias. *JAMA*. 1990;263(10):1392-1395.
17. Chan AW, Song F, Vickers A, et al. Increasing value and reducing waste: addressing inaccessible research. *Lancet*. 2014;383(9913):257-266.
18. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *New England Journal of Medicine*. 2008;358(3):252-260.

19. Goldacre B. Missing data. In: *Bad pharma*. Toronto: McClelland & Stewart; 2012:1-99.
20. McGauran N, Wieseler B, Kreis J, Schuler YB, Kolsch H, Kaiser T. Reporting bias in medical research - a narrative review. *Trials [Electronic Resource]*. 2010;11:37.
21. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet*. 2009;374(9683):86-89.
22. Moses H, 3rd, Matheson DH, Cairns-Smith S, George BP, Palisch C, Dorsey ER. The anatomy of medical research: US and international comparisons. *JAMA*. 2015;313(2):174-189.
23. Lexchin J. Sponsorship bias in clinical research. *Int J Risk Saf Med*. 2012;24(4):233-242.
24. Roehr B. GlaxoSmithKline is fined record \$3bn in US. *Bmj*. 2012;345:e4568.
25. GlaxoSmithKline to Plead Guilty and Pay \$3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data: Largest Health Care Fraud Settlement in U.S. History [press release]. United States Department of Justice, July 2, 2012.
26. Every-Palmer S, Howick J. How evidence-based medicine is failing due to biased trials and selective publication. *J Eval Clin Pract*. 2014;20(6):908-914.
27. Steinman MA, Bero LA, Chren MM, Landefeld CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann Intern Med*. 2006;145(4):284-293.
28. Amstutz A, Schandelmaier S, Frei R, et al. Discontinuation and non-publication of randomised clinical trials supported by the main public funding body in Switzerland: a retrospective cohort study. *BMJ Open*. 2017;7(7):e016216.

29. Johnson AL, Fladie I, Anderson JM, Lewis DM, Mons BR, Vassar M. Rates of Discontinuation and Nonpublication of Head and Neck Cancer Randomized Clinical Trials. *JAMA Otolaryngol Head Neck Surg.* 2020;146(2):176-182.
30. Kasenda B, von Elm E, You J, et al. Prevalence, characteristics, and publication of discontinued randomized trials. *JAMA.* 2014;311(10):1045-1051.
31. Ruegger CM, Dawson JA, Donath SM, Owen LS, Davis PG. Nonpublication and discontinuation of randomised controlled trials in newborns. *Acta Paediatrica.* 2017;106(12):1940-1944.
32. van den Bogert CA, Souverein PC, Brekelmans CT, et al. Non-Publication Is Common among Phase 1, Single-Center, Not Prospectively Registered, or Early Terminated Clinical Drug Trials. *PLoS ONE [Electronic Resource].* 2016;11(12):e0167709.
33. Yilmaz T, Gallagher MJ, Cordero-Coma M, et al. Discontinuation and nonpublication of interventional clinical trials conducted in ophthalmology. *Can J Ophthalmol.* 2020;55(1):71-75.
34. Emerson GB, Warne WJ, Wolf FM, Heckman JD, Brand RA, Leopold SS. Testing for the presence of positive-outcome bias in peer review: a randomized controlled trial. *Arch Intern Med.* 2010;170(21):1934-1939.
35. Song F, Loke Y, Hooper L. Why Are Medical and Health-Related Studies Not Being Published? A Systematic Review of Reasons Given by Investigators. *PLOS ONE.* 2014;9(10):e110418.
36. Cattapan A, Browne K, Halperin DM, et al. Motivation for participating in phase 1 vaccine trials: Comparison of an influenza and an Ebola randomized controlled trial. *Vaccine.* 2019;37(2):289-295.

37. Dhalla S, Poole G. Motivators to participation in medical trials: the application of social and personal categorization. *Psychol Health Med*. 2013;18(6):664-675.
38. McCann SK, Campbell MK, Entwistle VA. Reasons for participating in randomised controlled trials: conditional altruism and considerations for self. *Trials [Electronic Resource]*. 2010;11(31).
39. Moorcraft SY, Marriott C, Peckitt C, et al. Patients' willingness to participate in clinical trials and their views on aspects of cancer research: results of a prospective patient survey. *Trials [Electronic Resource]*. 2016;17(17).
40. Chalmers I, Glasziou P, Godlee F. All trials must be registered and the results published. *Bmj*. 2013;346(7890):8.
41. Connor JT. Positive reasons for publishing negative findings. *Am J Gastroenterol*. 2008;103(9):2181-2183.
42. Dowd MD. Breaching the contract: the ethics of nonpublication of research studies. *Arch Pediatr Adolesc Med*. 2004;158(10):1014-1015.
43. Hall R, de Antueno C, Webber A. Publication bias in the medical literature: a review by a Canadian Research Ethics Board. *Can J Anaesth*. 2007;54(5):380-388.
44. DeVito NJ, Bacon S, Goldacre B. Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study. *Lancet*. 2020;17:1-9.
45. Goldacre B, DeVito NJ, Heneghan C, et al. Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource. *Bmj*. 2018;362:k3218.
46. Ioannidis JP, Khoury MJ. Assessing value in biomedical research: the PQRST of appraisal and reward. *JAMA*. 2014;312(5):483-484.

47. Macleod MR, Michie S, Roberts I, et al. Biomedical research: increasing value, reducing waste. *Lancet*. 2014;383(9912):101-104.
48. Moher D, Naudet F, Cristea IA, Miedema F, Ioannidis JPA, Goodman SN. Assessing scientists for hiring, promotion, and tenure. *PLOS Biology*. 2018;16(3):e2004089.
49. Charmaz K. *Constructing grounded theory*. 2nd ed. Los Angeles: SAGE; 2014.
50. Glaser BG, Strauss AL. *Discovery of grounded theory: strategies for qualitative research*. New Brunswick, NJ: Aldine Transaction; 1967.
51. Starks H, Trinidad SB. Choose your method: A comparison of phenomenology, discourse analysis, and grounded theory. *Qualitative Health Research*. 2007;17(10):1372-1380.
52. Creswell JW. *Qualitative inquiry & research design: choosing among the five approaches*. Thousand Oaks, CA: Sage Publications; 2013.
53. Odutayo A, Emdin CA, Hsiao AJ, et al. Association between trial registration and positive study findings: cross sectional study (Epidemiological Study of Randomized Trials—ESORT). *Bmj*. 2017;356:j917.
54. Chalmers I. Underreporting research is scientific misconduct. *JAMA*. 1990;263(10):1405-1408.
55. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA*. 2010;303(1):47-53.
56. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med*. 2008;5(2):e45.

57. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine*. 2007;356(24):2457-2471.
58. *Staff report on GlaxoSmithKline and the diabetes drug Avandia*. United States Senate Committee on Finance; January 2010.
59. Expert Group on Phase One Clinical Trials: Final report.
https://webarchive.nationalarchives.gov.uk/20130105090249/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063117.
Published 2006. Accessed Sep 18, 2021.
60. Galsworthy MJ, Hristovski D, Lusa L, et al. Academic output of 9 years of EU investment into health research. *Lancet*. 2012;1380(9846):971-972.
61. Gordon D, Taddei-Peters W, Mascette A, Antman M, Kaufmann PG, Lauer MS. Publication of trials funded by the National Heart, Lung, and Blood Institute. *New England Journal of Medicine*. 2013;369(20):1926-1934.
62. Ahmer S, Haider I, Anderson D, Arya P. Do pharmaceutical companies selectively report clinical trial data? *Pakistan Journal of Medical Sciences*. 2006;22(3).
63. Kondro W, Sibbald B. Drug company experts advised staff to withhold data about SSRI use in children. *Cmaj*. 2004;170(5):783.
64. Song F, Parekh S, Hooper L, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess*. 2010;14(8):iii, ix-xi, 1-193.
65. Tamiflu campaign. BMJ. <https://www.bmj.com/tamiflu>. Published 2019. Accessed April 30, 2020.
66. Abbasi K. The missing data that cost \$20bn. *BMJ : British Medical Journal*. 2014;348.

67. Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. *Lancet*. 2006;367(9507):303-313.
68. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database Syst Rev*. 2014(4).
69. Angell M. Industry-sponsored clinical research: a broken system. *JAMA*. 2008;300(9):1069-1071.
70. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ : British Medical Journal*. 2014;348:g2545.
71. Chapman SJ, Shelton B, Mahmood H, Fitzgerald JE, Harrison EM, Bhangu A. Discontinuation and non-publication of surgical randomised controlled trials: observational study. *Bmj*. 2014;349(g6870).
72. Pica N, Bourgeois F. Discontinuation and Nonpublication of Randomized Clinical Trials Conducted in Children. *Pediatrics*. 2016;138(3).
73. Rees CA, Pica N, Monuteaux MC, Bourgeois FT. Noncompletion and nonpublication of trials studying rare diseases: A cross-sectional analysis. *PLoS Med*. 2019;16(11):e1002966.
74. Scott J, Cooper CM, Checketts JX, et al. An observational analysis of discontinuation and non-publication of osteoarthritis trials. *Osteoarthritis Cartilage*. 2018;26(9):1162-1169.
75. Yilmaz T, Jutten RJ, Santos CY, Hernandez KA, Snyder PJ. Discontinuation and nonpublication of interventional clinical trials conducted in patients with mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement (N Y)*. 2018;4:161-164.

76. Bodenheimer T. Uneasy alliance--clinical investigators and the pharmaceutical industry. *New England Journal of Medicine*. 2000;342(20):1539-1544.
77. Campa M, Ryan C, Menter A. Developing more open and equitable relationships with industry to improve advancements in clinical research in dermatology. *Br J Dermatol*. 2016;174(6):1365-1369.
78. Davidoff F, DeAngelis CD, Drazen JM, et al. Sponsorship, authorship, and accountability. *JAMA*. 2001;286(10):1232-1234.
79. Steinbrook R. Gag clauses in clinical-trial agreements. *New England Journal of Medicine*. 2005;352(21):2160-2162.
80. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. <http://www.icmje.org/recommendations/>. Updated Dec 2019. Accessed Sep 19,2021.
81. Mello MM, Clarridge BR, Studdert DM. Academic medical centers' standards for clinical-trial agreements with industry. *New England Journal of Medicine*. 2005;352(21):2202-2210.
82. Rochon PA, Sekeres M, Hoey J, et al. Investigator experiences with financial conflicts of interest in clinical trials. *Trials*. 2011;12(1).
83. Schulman KA, Seils DM, Timbie JW, et al. A national survey of provisions in clinical-trial agreements between medical schools and industry sponsors. *New England Journal of Medicine*. 2002;347(17):1335-1341.
84. Schafer A. Biomedical conflicts of interest: a defence of the sequestration thesis--learning from the cases of Nancy Olivieri and David Healy. *Journal of Medical Ethics*. 2004;30(1):8-24.

85. Naylor CD, Research Committee and Clinical Study Agreements Working Group of the Toronto Academic Health Science Council. Early Toronto experience with new standards for industry-sponsored clinical research: a progress report. *Cmaj*. 2002;166(4):453-456.
86. University of Toronto Governing Council. *Publication Policy*. Toronto: University of Toronto; May 30, 2007.
87. Lexchin J. *Private profits versus public policy: the pharmaceutical industry and the Canadian state*. Toronto: U of Toronto Press; 2016.
88. Tyers M, Brown E, Andrews DW, et al. Problems with co-funding in Canada. *Science*. 2005;308(5730):1867.
89. Djurisic S, Rath A, Gaber S, et al. Barriers to the conduct of randomised clinical trials within all disease areas. *Trials [Electronic Resource]*. 2017;18(1):360.
90. McLennan S, Griessbach A, Briel M, Making Randomized Trials Affordable (MARTA) Group. Practices and Attitudes of Swiss Stakeholders Regarding Investigator-Initiated Clinical Trial Funding Acquisition and Cost Management. *JAMA netw*. 2021;4(6):e2111847.
91. Gray GC. The ethics of pharmaceutical research funding: a social organization approach. *J Law Med Ethics*. 2013;41(3):629-634.
92. Merton R. The Normative Structure of Science. In: *The Sociology of Science: Theoretical and Empirical Investigations*. Chicago: University of Chicago Press; 1973:267-278.
93. Carroll HA, Toumpakari Z, Johnson L, Betts JA. The perceived feasibility of methods to reduce publication bias. *PLoS ONE [Electronic Resource]*. 2017;12(10):e0186472.

94. Malicki M, Marusic A, Consortium O. Is there a solution to publication bias? Researchers call for changes in dissemination of clinical research results. *J Clin Epidemiol*. 2014;67(10):1103-1110.
95. Lee KP, Boyd EA, Holroyd-Leduc JM, Bacchetti P, Bero LA. Predictors of publication: characteristics of submitted manuscripts associated with acceptance at major biomedical journals. *Med J Aust*. 2006;184(12):621-626.
96. Okike K, Kocher MS, Mehlman CT, Heckman JD, Bhandari M. Publication bias in orthopaedic research: an analysis of scientific factors associated with publication in the Journal of Bone and Joint Surgery (American Volume). *J Bone Joint Surg Am*. 2008;90(3):595-601.
97. Olson CM, Rennie D, Cook D, et al. Publication bias in editorial decision making. *JAMA*. 2002;287(21):2825-2828.
98. Roddick AJ, Chan FTS, Stefaniak JD, Zheng SL. Discontinuation and non-publication of clinical trials in cardiovascular medicine. *Int J Cardiol*. 2017;244:309-315.
99. Stefaniak JD, Lam TCH, Sim NE, Salman RAS, Breen DP. Discontinuation and non-publication of neurodegenerative disease trials: a cross-sectional analysis. *Eur J Neurol*. 2017;24(8):1071-1076.
100. Vrljicak Davidovic N, Tokalic R, Burilovic E, et al. Low dissemination rates, non-transparency of trial premature cessation and late registration in child mental health: observational study of registered interventional trials. *Eur Child Adolesc Psychiatry*. 2019;05:05.

101. Rosenthal R, Kasenda B, Dell-Kuster S, et al. Completion and Publication Rates of Randomized Controlled Trials in Surgery: An Empirical Study. *Annals of Surgery*. 2015;262(1):68-73.
102. Stefaniak JD, Lam TCH, Sim NE, Al-Shahi Salman R, Breen DP. Discontinuation and non-publication of neurodegenerative disease trials: a cross-sectional analysis. *Eur J Neurol*. 2017;24(8):1071-1076.
103. Abrams M, Bruijns SR, van Hoving DJ. Dissemination patterns of scientific abstracts presented at the first and second African Conference of Emergency Medicine. *Afr J Emerg Med*. 2019;9(2):101-105.
104. Bowers AM, Horn JG, Scott JT, Vassar MJ. Publication Rates in Podium and Poster Presentations at the 2012-2014 American Association of Hip and Knee Surgeons Annual Meetings. *J Arthroplasty*. 2017:1247-1252.e1241.
105. Chapman PB, Liu NJ, Zhou Q, et al. Time to publication of oncology trials and why some trials are never published. *PLoS ONE [Electronic Resource]*. 2017;12(9):e0184025.
106. Hanchanale S, Kerr M, Ashwood P, et al. Conference presentation in palliative medicine: predictors of subsequent publication. *BMJ support*. 2018;8(1):73-77.
107. Imani S, Moore G, Nelson N, Scott J, Vassar M. Publication rates of podium and poster abstract presentations at the 2010 and 2011 society of gynecologic oncology conferences. *Gynecol Oncol Rep*. 2018;24:6-9.
108. Meyer C, Fuller K, Scott J, Vassar M. Is publication bias present in gastroenterological research? An analysis of abstracts presented at an annual congress. *Peerj*. 2018;6:e4995.
109. Tritz D, Bautista L, Scott J, Vassar M. Conversion of Skeletal Society of Radiology annual meeting abstracts to publications in 2010-2015. *Peerj*. 2018;6:e5817.

110. Rice DB, Raffoul H, Ioannidis JPA, Moher D. Academic criteria for promotion and tenure in biomedical sciences faculties: cross sectional analysis of international sample of universities. *Bmj*. 2020;369:m2081.
111. Anonymous. Time to remodel the journal impact factor. *Nature*. 2016;535(7613):466.
112. Franzoni C, Scellato G, Stephan P. Science policy. Changing incentives to publish. *Science*. 2011;333(6043):702-703.
113. Tijdink JK, Schipper K, Bouter LM, Maclaine Pont P, de Jonge J, Smulders YM. How do scientists perceive the current publication culture? A qualitative focus group interview study among Dutch biomedical researchers. *BMJ Open*. 2016;6(2):e008681.
114. Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. *JAMA*. 1992;267(3):374-378.
115. Mann H. Research ethics committees and public dissemination of clinical trial results. *Lancet*. 2002;360(9330):406-408.
116. Strech D. Normative arguments and new solutions for the unbiased registration and publication of clinical trials. *J Clin Epidemiol*. 2012;65(3):276-281.
117. Meslin EM, Cho MK. Research ethics in the era of personalized medicine: updating science's contract with society. *Public Health Genomics*. 2010;13(6):378-384.
118. Jones CW, Braz VA, McBride SM, Roberts BW, Platts-Mills TF. Cross-sectional assessment of patient attitudes towards participation in clinical trials: does making results publicly available matter? *BMJ Open*. 2016;6(11):e013649.

119. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council. *Tri-council policy statement: ethical conduct for research involving humans*. December 2018.
120. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont report: ethical principles and guidelines for the protection of human subjects of research*. 1979.
121. Doshi P, Jefferson T, Del Mar C. The imperative to share clinical study reports: recommendations from the Tamiflu experience. *PLoS Med*. 2012;9(4):e1001201.
122. Herder M. Toward a jurisprudence of drug regulation. *J Law Med Ethics*. 2014;42(2):244-262.
123. Kesselheim AS, Mello MM. Confidentiality laws and secrecy in medical research: improving public access to data on drug safety. *Health Aff (Millwood)*. 2007;26(2):483-491.
124. Herder M. Reinstitutionalizing transparency at Health Canada. *Cmaj*. 2015;188(3):22.
125. Herder M. Denaturalizing Transparency in Drug Regulation. *McGill Journal of Law and Health*. 2015;8(2).
126. Turner EH. How to access and process FDA drug approval packages for use in research. *Bmj*. 2013;347:f5992.
127. Juni P, Reichenbach S, Egger M. COX 2 inhibitors, traditional NSAIDs, and the heart. *Bmj*. 2005;330(7504):1342-1343.
128. O'Connor AB. The need for improved access to FDA reviews. *JAMA*. 2009;302(2):191-193.

129. Goldacre B, Turner E, OpenTrials t. You can now search FDA approval documents easily at fda.opentrials.net. *Bmj*. 2017;356:j677.
130. Papathanasiou P, Brassart L, Blake P, et al. Transparency in drug regulation: public assessment reports in Europe and Australia. *Drug Discov Today*. 2016;21(11):1806-1813.
131. Kohler M, Haag S, Biester K, et al. Information on new drugs at market entry: retrospective analysis of health technology assessment reports versus regulatory reports, journal publications, and registry reports. *Bmj*. 2015;350:h796.
132. Mintzes B, Lexchin J, Quintano AS. Clinical trial transparency: many gains but access to evidence for new medicines remains imperfect. *Br Med Bull*. 2015;116:43-53.
133. Habibi R, Lexchin J. Quality and quantity of information in summary basis of decision documents issued by health Canada. *PLoS ONE [Electronic Resource]*. 2014;9(3):e92038.
134. European Medicines Agency widens public access to documents [press release]. London: European Medicines Agency, Nov 30, 2010.
135. Bruckner T. *Clinical trial transparency: a guide for policy makers*. Transparency International UK;2017.
136. Gotzsche PC, Jorgensen AW. Opening up data at the European Medicines Agency. *Bmj*. 2011;342(7808):1184-1186.
137. European Ombudsman. *Decision of the European Ombudsman closing his inquiry into complaint 2560/2007/BEH against the European Medicines Agency*. Nov 24, 2010.
138. Santos Quintano A, Bruckner T. *Clinical trials in the European Union: a roadmap to greater transparency*. Health Action International;2019.

139. Lexchin J, Herder M, Doshi P. Canada finally opens up data on new drugs and devices. *Bmj*. 2019;365:11825.
140. Government of Canada. Clinical information on drugs and health products. <https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/clinical-information-drugs-health-products.html>. Updated March 12, 2019. Accessed May 13, 2021.
141. Herder M, Doshi P, Lemmens T. Precedent pushing practice: Canadian court orders release of unpublished clinical trial data. *BMJ*. *BMJ Opinion Web site*. <https://blogs.bmj.com/bmj/2018/07/19/precedent-pushing-practice-canadian-court-orders-release-of-unpublished-clinical-trial-data/>. Updated Jul 19, 2018. Accessed Aug 1, 2020.
142. Doshi P, Jefferson T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. *BMJ Open*. 2013;3(2).
143. Gotzsche PC. Why we need easy access to all data from all clinical trials and how to accomplish it. *Trials [Electronic Resource]*. 2011;12:249.
144. Zarin DA, Tse T, Williams RJ, Carr S. Trial Reporting in ClinicalTrials.gov - The Final Rule. *New England Journal of Medicine*. 2016;375(20):1998-2004.
145. Chan AW, Pello A, Kitchen J, et al. Association of Trial Registration With Reporting of Primary Outcomes in Protocols and Publications. *JAMA*. 2017;318(17):1709-1711.
146. Emdin C, Odutayo A, Hsiao A, et al. Association of cardiovascular trial registration with positive study findings: Epidemiological Study of Randomized Trials (ESORT). *JAMA Intern Med*. 2015;175(2):304-307.

147. Rasmussen N, Lee K, Bero L. Association of trial registration with the results and conclusions of published trials of new oncology drugs. *Trials [Electronic Resource]*. 2009;10:116.
148. von Elm E, Meerpohl JJ. Trial results reporting: FDA Amendments Act Final Rule needs enforcement. *The Lancet*. 2020;395(10221):316-317.
149. How will national regulators in Europe impose fines for missing clinical trial results? TranspariMED. <https://www.transparimed.org/single-post/eu-clinical-trial-regulation-ctis-fines>. Updated Feb 25, 2021. Accessed Jun 5, 2021.
150. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0536&qid=1614070005812>. Accessed Jun 5, 2021.
151. US Food and Drug Administration. Notice of noncompliance issued pursuant to 42 U.S.C. 282(j)(5)(C)(ii). https://www.fda.gov/media/148036/download?utm_medium=email&utm_source=govdelivery. Updated Apr 27, 2021. Accessed Sep 18, 2021.
152. Pillar C. In a first, FDA cites violation of clinical trials reporting law. *Science*. doi:10.1126/science.abj2323.
153. FDA Takes Action For Failure to Submit Required Clinical Trial Results Information to ClinicalTrials.Gov. United States Food and Drug Administration. <https://www.fda.gov/news-events/press-announcements/fda-takes-action-failure-submit>

[required-clinical-trial-results-information-clinicaltrials.gov](https://www.fda.gov/oc/required-clinical-trial-results-information-clinicaltrials.gov). Updated Apr 28, 2021.

Accessed May 15, 2021.

154. Angell M. *The truth about the drug companies: how they deceive us and what to do about it*. New York: Random House; 2004.
155. DeAngelis CD, Fontanarosa PB. Impugning the integrity of medical science: the adverse effects of industry influence. *JAMA*. 2008;299(15):1833-1835.
156. Gotzsche PC. Patients not patents: Drug research and development as a public enterprise. *European Journal of Clinical Investigation*. 2018;48(2).
157. Light DW, Lexchin J, Darrow JJ. Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs. *Journal of Law Medicine & Ethics*. 2013;41(3):590-600.
158. Rennie D. When evidence isn't: trials, drug companies and the FDA. *Journal of Law and Policy*. 2007;15(3).
159. Rodwin MA. Independent clinical trials to test drugs: the neglected reform. *St Louis U J Health L and Poly*. 2012;6(113):113-166.
160. Goldacre B, Lane S, Mahtani KR, et al. Pharmaceutical companies' policies on access to trial data, results, and methods: audit study. *Bmj*. 2017;358:j3334.
161. Strom BL, Buyse M, Hughes J, Knoppers BM. Data sharing, year 1--access to data from industry-sponsored clinical trials. *New England Journal of Medicine*. 2014;371(22):2052-2054.
162. Vaduganathan M, Nagarur A, Qamar A, et al. Availability and Use of Shared Data From Cardiometabolic Clinical Trials. *Circulation*. 2018;137(9):938-947.

163. Doshi P. From promises to policies: is big pharma delivering on transparency? *Bmj*. 2014;348:g1615.
164. Le Noury J, Nardo JM, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *Bmj*. 2015;351:h4320.
165. Zarin DA, Fain KM, Dobbins HD, Tse T, Williams RJ. 10-Year Update on Study Results Submitted to ClinicalTrials.gov. *New England Journal of Medicine*. 2019;381(20):1966-1974.
166. CIHR Signs the World Health Organization's Joint Statement on Public Disclosure of Results from Clinical Trials [press release]. Canadian Institutes of Health Research, Dec 21, 2021.
167. San Francisco Declaration on Research Assessment. American Society for Cell Biology. <https://sfdora.org/read/>. Updated Dec 16, 2012. Accessed May 7, 2021.
168. Canadian Institutes of Health Research. Revised Grants Evaluation Criteria – Interpretation Guidelines. <https://cihr-irsc.gc.ca/e/39913.html>. Updated Dec 11, 2009. Accessed Jun 13, 2021.
169. Canadian Institutes of Health Research. Peer Review Manual – Project. <https://cihr-irsc.gc.ca/e/49564.html>. Updated April 15, 2021. Accessed May 7, 2021.
170. DeVito NJ, French L, Goldacre B. Noncommercial funders' policies on trial registration, access to summary results, and individual patient data availability. *JAMA*. 2018;319(16):1721-1723.
171. Kolstoe SE, Shanahan DR, Wisely J. Should research ethics committees police reporting bias? *BMJ (Clinical research ed)*. 2017;356:j1501.

172. Savulescu J, Chalmers I, Blunt J. Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. *Bmj*. 1996;313(7069):1390-1393.
173. Keyes A, Mayo-Wilson E, Nuamah P, Lalji A, Tetteh O, Ford DE. Creating a Program to Support Registering and Reporting Clinical Trials at Johns Hopkins University. *Acad Med*. 2021;96(4):529-533.
174. O'Reilly EK, Hassell NJ, Snyder DC, et al. ClinicalTrials.gov reporting: strategies for success at an academic health center. *Clin Transl Sci*. 2015;8(1):48-51.
175. Kondro W, Sibbald B. Drug company experts advised staff to withhold data about SSRI use in children. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2004;170(5):783.
176. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. *Academic medicine : journal of the Association of American Medical Colleges*. 2014;89(9):1245-1251.
177. ClinicalTrials.gov. United States National Library of Medicine. <https://clinicaltrials.gov/>. Accessed Mar 24, 2019.
178. Canadian Clinical Trials Asset Map. Canadian Clinical Trials Coordinating Centre. <https://www.cctam.ca/>. Accessed Mar 23, 2019.
179. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council. Tri-Agency Guide on Financial Administration. https://nserc-crsng.gc.ca/InterAgency-Interorganismes/TAFA-AFTO/guide-guide_eng.asp#25. Updated Nov 27, 2020. Accessed May 9, 2021.

180. *ATLAS.ti* [computer program]. Version 8: ATLAS.ti Scientific Software Development GmbH.
181. Cowley AJ, Skene A, Stainer K, Hampton JR. The effect of lorcaïnide on arrhythmias and survival in patients with acute myocardial infarction: an example of publication bias. *Int J Cardiol.* 1993;40(2):161-166.
182. Evidence-Based Medicine DataLab. Who's sharing their clinical trial results? <https://fdaaa.trialstracker.net/>. Updated Mar 19, 2021. Accessed Mar 20, 2021.
183. Boyd K. Commentary: Early discontinuation violates Helsinki principles. *BMJ (Clinical research ed).* 2001;322(7286):605-606.
184. Lievre M, Menard J, Bruckert E, et al. Premature discontinuation of clinical trial for reasons not related to efficacy, safety, or feasibility. *BMJ (Clinical research ed).* 2001;322(7286):603-605.
185. Psaty BM, Rennie D. Stopping medical research to save money: a broken pact with researchers and patients. *JAMA.* 2003;289(16):2128-2131.
186. Hoeg RT, Lee JA, Mathiason MA, et al. Publication outcomes of phase II oncology clinical trials. *Am J Clin Oncol.* 2009;32(3):253-257.
187. Timmer A, Hilsden RJ, Cole J, Hailey D, Sutherland LR. Publication bias in gastroenterological research - a retrospective cohort study based on abstracts submitted to a scientific meeting. *BMC Med Res Methodol.* 2002;2:7.
188. Institute of Medicine. *Sharing clinical trial data: maximizing benefits, minimizing risk.* Washington, DC: The National Academies Press; 2015.

189. Snider SH, Flume PA, Gentilin SL, Lesch WA, Sampson RR, Sonne SC. Overcoming non-compliance with clinical trial registration and results reporting: One Institution's approach. *Contemporary clinical trials communications*. 2020;18:100557.
190. Canadian research funding organizations sign San Francisco Declaration on Research Assessment (DORA). Canadian Institutes of Health Research. <https://cihr-irsc.gc.ca/e/51732.html>. Updated Mar 5, 2020. Accessed Sep 18, 2021.
191. Spence O, Onwuchekwa Uba R, Shin S, Doshi P. Patient consent to publication and data sharing in industry and NIH-funded clinical trials. *Trials [Electronic Resource]*. 2018;19(1):269.
192. Canadian Institutes of Health Research. Governing Council - Members. Government of Canada. <https://cihr-irsc.gc.ca/e/6953.html>. Updated Sep 23, 2021. Accessed Dec 9, 2021.
193. Baylis F, Lemmens T, Herder M. *Letter to Secretariat on Responsible Conduct of Research on proposed revisions to TCPS2 (2014)*. February 7, 2017.
194. Joint statement on public disclosure of results from clinical trials. World Health Organization. <https://www.who.int/news/item/18-05-2017-joint-statement-on-registration>. Updated May 18, 2017. Accessed Jan 8, 2021.
195. Health Research Authority. Make it Public: transparency and openness in health and social care research. <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/research-transparency/make-it-public-transparency-and-openness-health-and-social-care-research/>. Updated Oct 11, 2021. Accessed Dec 27, 2021.

196. World first: UK starts monitoring all clinical trials to check if they report results. TranspariMED. <https://www.transparimed.org/single-post/make-it-public-hra>. Updated Sep 17, 2021. Accessed Dec 27, 2021.
197. Lane S, Baggaley L, DeVito NJ. *AllTrials report to the House of Commons Science and Technology inquiry into research integrity: clinical trials transparency. Update on compliance of UK university and NHS trust compliance with obligations to report clinical trial results*. AllTrials;2019.
198. Report of the European Ombudsman conference - Access to EU documents: what next? European Ombudsman. <https://www.ombudsman.europa.eu/en/event-document/en/149745>. Updated Nov 28, 2021. Accessed Dec 30, 2021.
199. European Medicines Agency. European Medicines Agency policy on publication of clinical data for medicinal products for human use. https://www.ema.europa.eu/en/documents/other/european-medicines-agency-policy-publication-clinical-data-medicinal-products-human-use_en.pdf. Updated Mar 21, 2019. Accessed Dec 18, 2021.
200. Shuchman M. Health Canada's new clinical trials database should be mandatory, says expert. *Cmaj*. 2013;185(11):946.
201. Fierlbeck K. Transparency, pharmaceuticals, and the problem of policy change. In: Fierlbeck K, Graham J, Herder M, eds. *Transparency, power, and influence in the pharmaceutical industry*. Toronto: University of Toronto Press; 2021:13-62.
202. Hoffmann T, Glasziou P, Beller E, Goldacre B, Chalmers I. Focus on sharing individual patient data distracts from other ways of improving trial transparency. *Bmj*. 2017;357:j2782.

203. Riveros C, Dechartres A, Perrodeau E, Haneef R, Boutron I, Ravaud P. Timing and completeness of trial results posted at ClinicalTrials.gov and published in journals. *PLoS medicine*. 2013;10(12):e1001566-e1001566.
204. Canadian Institutes of Health Research. CIHR Grants and Awards Guide. <https://cihr-irsc.gc.ca/e/22631.html>. Updated May 22, 2018. Accessed May 9, 2021.
205. Canadian Institutes of Health Research. Canadian Institutes of Health Research (CIHR) Application Administration Guide. <https://cihr-irsc.gc.ca/e/50805.html>. Published 2019. Accessed May 9, 2021.
206. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council. *Tri-Agency Framework: Responsible Conduct of Research (2016)*. Ottawa, ON.
207. Canadian Institutes of Health Research. Peer Review Manual - Foundation. <https://cihr-irsc.gc.ca/e/48486.html>. Updated Oct 1, 2018. Accessed May 7, 2021.
208. Canadian Institutes of Health Research. CIHR Peer Review Guide for Training and Salary Awards. <https://cihr-irsc.gc.ca/e/23467.html#a9>. Updated Nov 14, 2019. Accessed May 8, 2021.
209. Canadian Institutes of Health Research. CIHR Reviewers' Guide for New Investigator Salary Awards. <https://cihr-irsc.gc.ca/e/41208.html>. Updated Nov 14, 2019. Accessed May 8, 2021.
210. Canadian Institutes of Health Research. CIHR Reviewers' Guide for Doctoral Research Awards. <https://cihr-irsc.gc.ca/e/33043.html>. Updated Jul 28, 2020. Accessed May 8, 2021.

211. Canadian Institutes of Health Research. CIHR Reviewers' Guide for Fellowship Awards. <https://cihr-irsc.gc.ca/e/26720.html>. Updated Sep 1, 2020. Accessed May 8, 2021.
212. Canadian Institutes of Health Research. Peer review: Policies and procedures. <https://cihr-irsc.gc.ca/e/39414.html>. Updated Aug 22, 2017. Accessed May 8, 2021.
213. Canadian Institutes of Health Research. CIHR Peer Review Manual for Clinician Scientist Award Applications. https://cihr-irsc.gc.ca/e/documents/peer_review_manual_clinician_scientist_e.pdf. Updated January 2014. Accessed May 7, 2021.

Appendices

These appendices contain interview guides for each type of participant (**Appendix A**) and responses received in correspondence with CIHR (**Appendix B**).

Appendix A Interview guides

Interview guides are included below for clinical trial investigators, research administrators, REB members, and clinical trial participants.

A.1 Interview guide for clinical trial investigators

Clinical trials are important for developing new drugs and providing the best medical care. However, about 4 in every 10 clinical trials are not published or only published after a long delay.³ In this study, I am interested in trying to better understand this phenomenon, in part by talking to trial investigators about their experiences and views related to trials and trial reporting.

1. Introductory questions

- a. Could you tell me about the types of trials that you do? (e.g., research areas, phase of trials, single or multi-site trials, funding source)
- b. How much of your work involves conducting clinical trials? If this is only part of your work, how does it fit into your other work? (e.g., clinical practice, teaching, administration)
- c. Could you describe your typical role and responsibilities when conducting a clinical drug trial? (e.g., Principal Investigator/ co-investigator, trial design, recruiting patients, administering treatment, collecting data, reporting findings, grant-writing, liaising with sponsor)
- d. Optional, time-permitting: When you are conducting a trial, who would you typically have occasion to interact with during the course of a trial, from the planning to implementation and reporting? (e.g., co-investigators, clinical research coordinator, clinical research associate or monitor from contract research organization, project manager from contract research organization, patients)

2. Specific clinical drug trial

- a. Could I ask you to think about an example of a trial you were involved with as an investigator, which concluded prior to the last 12 months?
- b. Could you describe the trial?
 - o Purpose of the trial (e.g., research question, drug, health condition, importance)

- Generally how was it designed? (e.g., multi-site or single site, phase of trial, study population, intervention and control group, randomization, blinding, duration)
 - How was the trial funded? (e.g., industry, non-industry grant, unfunded)
- c. Experience of the trial
- How did this trial come about?
 - Could you talk about your role and responsibilities in this trial?
 - How would you describe the experience of conducting this trial? (design, recruitment, treating patients, collecting data, interactions with others, etc.)
 - What were some things that went well in this trial? What were some challenges in this trial? (e.g., recruitment, treatment, analysis, reporting)
 - Was the trial completed? If so, when did the trial conclude (i.e., year and month)? (Could I ask what the main findings were?) If not, could you describe the factors that led to stopping the trial?
- d. Have the results of this trial been disseminated to the scientific community? If so, in what ways? (e.g., conference presentations, peer-reviewed publications, trial registry) Was the trial registered in clinicaltrials.gov or another registry?
- If the results have been reported in a registry or peer-reviewed journal: Could you talk about the events leading to the publication of the trial findings? (e.g., steps involved, any barriers or challenges) How long after trial completion were results reported?
 - If the results have not been reported in a registry or peer-reviewed journal (more than 1 year following completion of the trial): It is relatively common that results from a trial are not published. Could you talk about events leading to the trial findings not being reported in this particular case? (For example, in comparison to trials you have been involved with that were published, what differed in this trial?)
3. Experience in other clinical drug trials
- a. If the trial discussed above was not published
- Was your experience in the trial you just described typical or different from other trials you have been involved with, particularly with respect to delays or challenges in reporting the trial results? Could you provide an example? (purpose, design, role, experience, recruitment, treatment, analysis, results, reporting, interactions with others)
- b. If the trial discussed above was published
- Could I ask whether you have participated as an investigator in trials for which the findings were not published in either a registry or peer-reviewed journal (1 or 2 years after trial completion)?
 - It is relatively common that results from a trial are not published. If we consider a trial you participated in that was not published, could you talk about events leading to the trial findings not being reported? (For example, in comparison to the trial you described above, what differed in this trial?)

- Was your experience in the trial you just described typical or different from other trials you have been involved with, particularly with respect to delays or challenges in reporting the trial results? Could you provide an example?
 - c. In your experience as a trialist, have you encountered (or could you talk more about) barriers to reporting the trial's findings? If so, could you describe those? (e.g., difficulties with co-investigators, constraints in clinical trial agreements or informal influences from a sponsor)
 - d. Optional, time-permitting: Are you aware of instances in which colleagues have conducted trials and the results have not been reported? Could you describe an example? Could you talk about events leading to the results not being published? Are you aware of (or could you talk more about) barriers to reporting trial results that have been experienced by colleagues? (Could you give an example?)
 - e. Possible follow-up questions, if applicable:
 - How was the decision made on whether to publish?
 - Was the sponsor able to influence the decision to publish? If so, how did this occur? (clinical trial agreement, control of data, funding dependency)
 - In your experience of multi-site trials, is a given site allowed access to data from other sites? Does this differ between industry and investigator-initiated trials?
 - Could you talk more about an investigator's incentive to publish positive vs. negative findings?
4. Addressing the issue of unpublished trials
- a. In your view, how important is it to address the issue that many trials are not published, or not published within 1 or 2 years of trial completion?
 - Could you explain why you think that?
 - Do you feel there is a responsibility to the trial participant to ensure that trials are published?
 - b. What do you think would help ensure that trial results are published? (e.g., resources, policies, education)
 - For example, in the unpublished trials that you or your colleagues have participated in, can you think of something that might have helped ensure that a trial was reported?
 - Based on your experience, do you have any advice for clinical investigators for navigating challenges or barriers to reporting trial results?
 - c. Similarly, what role would you envision for others to help ensure that clinical trials are reported:
 - Research ethics boards?
 - Administrators at universities or other research institutions?
 - Health Canada?
 - d. As academic or career incentives may be related to delays in publication or whether results are reported, do you think anything could be done to change incentives?

5. Additional comments
 - a. Is there something we have not talked about that would help me to understand the experience of conducting a clinical trial?
 - b. Similarly, is there something we have not talked about that would contribute to understanding of the phenomenon of unpublished trials?

Short-answer questions (Based on background questions from survey by Rochon et al 2011.)⁸²

6. Could you describe your primary appointment?
 - a. University or academic teaching hospital
 - b. Non-academic community-based hospital
 - c. Other (e.g., private practice, cancer centre, pharmaceutical)
7. How many years' experience do you have in conducting clinical trials?
 - a. ≤ 5 years
 - b. > 5 years
8. What types of funding have the trials you have conducted had?
 - a. Non-industry trials only
 - b. Industry trials only
 - c. Both industry and non-industry trials
9. What is the most senior role you have had in a clinical trial?
 - a. Principal investigator for the entire trial
 - b. Principal investigator for site
 - c. Other
10. Have you conducted the following types of trials?
 - a. Only single site trials
 - b. Only multiple site trials
 - c. Both single and multiple site trials

A.2 Interview guide for research administrators

Clinical trials are important for developing new drugs and providing the best medical care. However, about 4 in every 10 clinical trials are not published or only published after a long delay.³ In this study, I am interested in trying to better understand this phenomenon, in part by talking to trial investigators and research administrators about their experiences and views related to trials and trial reporting.

What follows include questions for (1) administrators involved in oversight of clinical research, and (2) administrators involved with oversight, review or negotiation of clinical trial agreements

or other agreements with industry sponsors. Questions specific primarily to one of these groups are denoted A1 or A2, respectively.

1. Introductory questions

- a. Could you describe your experience with
 - A1: Administration of research including clinical trials? (Do you also have experience conducting clinical trials? If so, could you describe your experience conducting clinical trials?)
 - A2: Review, drafting or negotiation of clinical trial agreements with industry funders?
- b. What is your current role and responsibilities with respect to involvement in
 - A1: Administration of research including clinical trials?
 - A2: Clinical trial agreements (CTAs) with industry funders? What types of clinical trial agreements are you involved with? (e.g., CTAs for industry-sponsored trials, CTAs for investigator-initiated trials with industry funding)

2. Research institution policies on dissemination of trial research (A1)

- a. In your view, does your research institution have a role in ensuring that the results of trials conducted at your institution or affiliated institutions are published? How do you see your institution's role in that?
- b. Does your research institution have a policy to require trial registration? Does policy also require reporting of findings in a trial registry or in a peer-reviewed journal? If so, is reporting required to occur within a particular timeframe?
- c. Does your research institution monitor the proportion of clinical trials conducted at your institution that are published in a timely way or do other monitoring of trial reporting?
- d. Does your research institution have other types of policies to try to ensure that trials conducted at your institution or affiliated institutions are published?
- e. Has your research institution considered introducing such policies or additional policies? Could you elaborate on the types of policies considered?

3. Clinical trial agreements (A2)

- a. Review of agreements
 - Does your research institution require that clinical trial agreements between researchers and funders of clinical trials be reviewed by the institution? Are you aware of whether there are sometimes publication agreements with industry funders separate from clinical trial agreements? If so, would your institution also review the publication agreements?
 - For university administrators: If an investigator affiliated with the university is involved in a clinical trial with industry funding, would the CTA typically be reviewed by your office? Are there cases where the CTA would only be reviewed by a hospital affiliated with the university?
- b. For CTAs for clinical trials of pharmaceutical drugs, who would the parties to the agreement typically be? For example, would the industry partner typically be a drug company or a contract research organization? (Are independent academic research organizations sometimes involved?)

- c. Does your research institution allow clauses in clinical trial agreements with industry relating to clinical trials in which:
 - The funder can decide on whether trial results are published? If so, how common would that be in CTAs for industry-sponsored trials (or in investigator-initiated trials that have industry funding)?
 - The funder can delay publication of trials results? If so, what types of delays are permitted in terms of duration and rationale? (e.g., delays of 6 months to seek patent protection for a drug)
- d. Ownership of data and access to data
 - Does your research institution allow clauses in clinical trial agreements with industry in which the funder would have ownership of the data? How common would it be for the industry funder to own the data in industry-sponsored clinical trials? Does this differ in investigator-initiated trials that have industry funding, as compared to industry-sponsored trials?
 - If so, in the context of a multi-site trial, how common would it be for the clinical trial agreement with industry to specify that investigators have access to data collected from all sites of the trial? Again, does this differ in investigator-initiated trials that have industry funding, as compared to industry-sponsored trials? In CTAs for multi-site trials, how is the issue of access to data from all sites by investigators typically addressed, if at all? (e.g., who has access, process for accessing data from all sites)
 - Are you aware of contracts which specify that an academic research organization would be part of the study organization in an industry-sponsored study and must have an identical copy of the study database? (to allow shared data access and validation of analyses conducted by the sponsor)
- e. Protection of the right to publish trial results
 - Do some clinical trial agreements require publication of trial results in a peer-reviewed journal or trial registry? (in investigator-initiated trials with industry funding, in industry-sponsored trials)
 - Does your institution require language to be included in clinical trial agreements with industry that would protect the investigator's right to publish clinical trial results? What type of language is required?
 - If language is required that would protect the investigator's right to publish: In the context of a multi-site trial, would the investigator's right to publish trial results apply only to data from the local site or would it include the right to publish results based on all of the data collected in the trial? Would this apply to industry trials or only investigator-initiated trials with industry funding?
 - Does your institution require language to be included in clinical trial agreements with industry to set out timelines for publication? If so, what would need to be specified?
- f. Do you feel that clinical trial agreements (or other agreements such as publication agreements) between your research institution and industry provide sufficient protection of the right to publish clinical trial results? Or do you feel this could be strengthened?

- g. Are you aware of difficulties or challenges in negotiating clinical trial agreements with industry? Could you describe some of the challenges?
 - h. Publication agreements. If publication agreements are reviewed, what issues are typically addressed in the publication agreement and how do these compare with CTAs?
 - i. Some investigators have expressed that industry funders can sometimes influence the decision to publish clinical trial findings. Do you have thoughts on how clinical trial agreements may help create the context for that to occur?
4. Experience or examples related to dissemination of research (A1)
- a. It is relatively common that results from clinical trials are not published. Could I ask if you have become aware of cases of unpublished trials at your research institution during your time as an administrator? If so, could you describe an example?
 - b. In your view, how does the case you have described relate more generally to policies or practices at your research institution with respect to dissemination of trial research? Would you say the case you described reflects a pattern?
 - c. Are you aware of cases where investigators from your research institution have had difficulties with industry funders in relation to publishing of trial findings? Could you describe a case? Again, how would you relate this case to policies or practices at your research institution with respect to dissemination of trial research?
5. Academic or career incentives (A1)
- Some trial investigators I have spoken to have expressed the view that there is a stronger incentive to publish trials with positive findings as compared to negative trials. For example, positive trials might be more likely to lead to additional grant funding, and there is a perception among some investigators that positive trials are easier to publish in prestigious journals, which could help their careers.
- a. In your view, is it possible that trial investigators at your research institution have a stronger incentive to publish positive trials as compared to negative trials?
 - b. Do you think that it would be worthwhile to try to change incentives in a way which might encourage full reporting of trials? If so, how might this be done?
6. Addressing the issue of unpublished trials
- a. A1: In your view, how important is it to address the issue that many trials are not published, or not published within 1 or 2 years of trial completion?
 - o Could you explain why you think that?
 - o Do you feel there is a responsibility to the trial participant to ensure that trials are published?
 - b. A1/A2: Are there policies or actions your research institution, or other research institutions, could take to better address the need for trial findings to be disseminated? Could you elaborate on those?
 - c. A1/A2: Are there policies or actions that could be taken by others to help ensure that clinical trials are reported, such as:
 - o Research ethics boards?
 - o Health Canada?

- d. A1/A2: Are there policies at your research institution that it might be useful for me to review to understand issues relating to trial reporting and/or clinical trial agreements?

7. Additional comments (A1/A2)

Is there something we have not talked about that would contribute to understanding of policy issues regarding trial reporting?

Short-answer questions (A1/A2) (Based on background questions from survey by Rochon et al 2011.)⁸²

- 8. Could you describe your primary appointment?
 - a. University or academic teaching hospital
 - b. Non-academic community-based hospital
 - c. Other (e.g., private practice, cancer centre, pharmaceutical)
- 9. How many years' experience do you have either in administration at a research institution that conducts clinical trials?
 - a. ≤ 5 years
 - b. > 5 years

A.3 Interview guide for clinical research ethics board members

Clinical trials are important for developing new drugs and providing the best medical care. However, about 4 in every 10 clinical trials are not published or only published after a long delay.³ In this study, I am interested in trying to better understand this phenomenon, in part by talking to members of research ethics boards about experiences and relevant policies.

- 1. Introductory questions
 - a. Could I ask you how long you have been involved with ethics review of clinical trials?
 - b. Could you describe your current role in ethics review of clinical trials? Has your role changed over time, since you became involved?
 - c. Do you also have experience conducting clinical trials? If so, could you describe your experience conducting clinical trials?
- 2. Review of clinical trials and clinical trial reporting
 - a. Could I ask you to describe the typical process for review of a clinical trial, from your point of view as an REB member (for example, in relation to a clinical drug trial that has come before the REB)? (documents, key questions, discussion, time required)
 - b. Does the REB have a policy to require registration of clinical trials prior to enrolment of patients? If so, does the REB require that the trial be registered as a condition of ethics approval?
 - c. Does the REB require that trial results are reported in a trial registry or in a peer-reviewed journal? If so, is reporting required to occur within a particular timeframe?

- d. Does the REB track whether each trial has been registered and whether results have been reported in a registry or peer-reviewed journal? If so, are you aware of whether the REB monitors the proportion of trials that have been registered and/or have reported results in registries or peer-reviewed journals?
 - e. Are the past practices of investigators in terms of clinical trial registration or reporting considered at the time of ethics review for a clinical trial?
3. Protocols, contracts and other agreements with funders
- a. Responsibility for review
 - o Does the REB review not only protocols but also contracts and other agreements between clinical trial investigators and funders?
 - o Or is review of contracts and other agreements delegated to others at your research institution? If so, who has responsibility for reviewing these?
 - o If responsibilities are divided, are the agreements reviewed for consistency periodically?
 - b. Does the REB/ your research institution allow clauses in protocols, or clinical trial agreements with industry funders, in which:
 - o The funder can decide on whether trial results are published?
 - o The funder would have ownership of the data and may not give permission to site investigators to access all of the data collected in the trial?
 - o The funder can delay publication of trials results? If so, what types of delays are permitted in terms of duration and rationale? (e.g., delays of 6 months to seek patent protection for a drug)
 - c. Protection of the right to publish trial results
 - o Does the REB/ your research institution require language to be included in protocols or clinical trial agreements with industry that would protect the investigator's right to publish clinical trial results? What type of language is required?
 - o If language is required that would protect the investigator's right to publish: In the context of a multi-site trial, would the investigator's right to publish trial results apply only to data from the local site or would it include the right to publish results based on all of the data collected in the trial? Would this apply to industry trials or only investigator-initiated trials with industry funding?
 - o Does the REB/ your research institution require language to be included in protocols or clinical trial agreements with industry to set out timelines for publication? If so, what would need to be specified?
 - d. Do you feel that protocols, or clinical trial agreements between your research institution and industry, provide sufficient protection of the right to publish clinical trial results? Or do you feel this could be strengthened?
4. Experience related to dissemination of research
- a. It is relatively common that results from clinical trials are not published. Could I ask whether, in your experience as an REB member, you have become aware of clinical trials that have not be published? If so, could you describe an example?

- b. In your view, how does the case you have described relate more generally to policies or practices at the REB/ your research institution with respect to dissemination of trial research? Would you say the case you described reflects a pattern?
 - c. Potential influence of industry funders
 - Are you aware of cases where investigators from your research institution have had difficulties with industry funders in relation to publishing of trial findings? Could you describe a case? Again, how would you relate this case to policies or practices at the REB/ your research institution with respect to dissemination of trial research?
 - In your experience in ethics review, have you seen protocols or clinical trial agreements for industry-funded trials that may constrain full reporting of clinical trial results? If so, could you describe an example? Could this still occur or would current policy or practices likely prevent this?
 - In your experience, have observed other barriers to publications due to influence of industry funders? If so, could you describe an example? Could this still occur or would current policy or practices likely prevent this?
5. Addressing the issue of unpublished trials
- a. In your view, how important is it to address the issue that many trials are not published, or not published within 1 or 2 years of trial completion?
 - Could you explain why you think that?
 - Do you feel there is a responsibility to the trial participant to ensure that trials are published?
 - Do you think this relates to informed consent or other aspects of research ethics?
 - b. How do you view the role of REBs, if any, in addressing the issue of unpublished trials? Are there other policies or actions that could be taken on this issue? What barriers to such policies or actions exist, or what could facilitate these?
 - c. Are there policies or actions that could be taken by others to help ensure that clinical trials are reported, such as:
 - Others at research institutions?
 - Health Canada?
 - d. Is there something we have not talked about that would help contribute to understanding why many trials are not published or the role of the REB in addressing this?

Short-answer questions

How many years' experience do you have as a member of an REB?

- c. 1 to 2 years
- d. 3 to 5 years
- e. >5 years

A.4 Interview guide for clinical trial participants

1. Involvement and expectations
 - a. How did you come to be involved in the trial? (e.g., sought trial to participate in, invited by physician, saw advertisement; change in health condition)
 - b. How did you understand the purpose of the trial? (e.g., drug, health condition, research question, outcomes, efficacy, safety and efficacy for regulatory approval, postmarket safety)
 - c. How would you describe what motivated you to enroll in the trial?
 - o How important did you feel it was to get access to the treatment?
 - o How important did you feel it was that it might help future patients?
 - o How important were other factors in your decision to enroll in the trial? (e.g., having your health monitored closely, having a good relationship with your physician)
 - d. Do you recall how you felt about enrolling in the trial? What were your expectations of the trial?
 - e. What did you understand about how the trial was designed? (e.g., controlled or not, placebo or comparison drug, randomization, blinding, duration of treatment, study population) What did you understand to be the potential benefits or risks of participation?
 - f. How was information about the purpose, design and benefits or risks of participation in the trial communicated to you?
2. Activities in the trial
 - a. When did your participation in the trial begin and end?
 - b. What did participating in the trial involve? (e.g., taking medication, clinic visits or medical tests)
 - c. Did you receive the trial medication from your regular physician? Who did you interact with as part of the trial? (e.g., clinical research coordinator, regular physician, other physician or nurses)
 - d. What did participating require of you, in comparison to your prior therapy or routine? (e.g., travel to clinic, investment of time)
3. Experience of trial
 - a. How would you describe the experience of participating in the trial? (e.g., what was it like to participate in the trial, what did you think of the experience at the time, how did it feel to participate in the trial)
 - b. Did you feel you benefited from participating in the trial? In what ways? (e.g., health benefits, satisfaction)
 - c. Did you feel you experienced any adverse effects from the treatment or participation in the trial? How would you describe these effects? (e.g., health effects, stress)
 - d. Did you complete the treatment in the trial? If not, what led to withdrawal from the trial?

- e. Are you aware of whether the trial has concluded? Do you know when it was (or was expected to be) concluded?

4. Reporting of trial results

Clinical trials are important for developing new drugs and providing the best medical care. However, about 4 in every 10 clinical trials are not published or only published after a long delay.³ When clinical drug trials remain unpublished, they are unavailable to the larger wider scientific community. This makes it harder for researchers, doctors and others to understand which drugs are safe and effective.

a. If the trial has concluded:

- Were you informed about the results of the trial? If so, how did this occur? How did you feel about being informed about trial findings (or about not being informed)?
- Are you aware of whether results of the trial have been published?
 - If aware, how did you become aware of this? How do you feel about the fact the results were published / were not published?
 - If not aware, how do you think you would feel if the results of the trial were not published?

b. If the trial has not concluded:

- How do you think you would feel if the results of the trial were not published?

c. Importance of reporting and of participants being informed of results:

- Given your experience as a trial participant, how would you describe the importance of whether trial results are published? Could you explain why you think that?
- How would you describe the importance of trial participants being informed of the results of the trial they participated in? If you feel this to be important, what do you think would be a good way to communicate the findings to participants? (e.g., summary in lay language or information shared by physician)

d. Additional comments:

- Is there something we have not talked about that you think I should know to understand your experience of the trial?
- Similarly, is there something we have not discussed that you think I should know to understand your views on the publication of trial results?

Short answer questions

5. Could I ask you to tell me your age? (<30 years, 30-39, 40-49, 50-64, >=65)
6. Could I ask you the highest level of education that you have completed? (<= grade 8, high school, community college, university, graduate school)

Appendix B Questions sent to Canadian Institutes of Health Research and replies

A member of the research team (RM) sent initial questions and assessments of each question to the Canadian Institutes of Health Research (CIHR) via the Secretariat on Responsible Conduct of Research (SRCR) of the Government of Canada in May 2021. A reply was received later the same month, including responses from SRCR and CIHR. (**Table 5**) (SRCR is a tri-Agency group, or in other words an agency of CIHR, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council.) RM sent follow-up questions to the CIHR Contact Centre in June 2021, and a reply to these questions were received later that month. (**Table 6**)

Table 5. Initial questions and assessments sent to the Canadian Institutes of Health Research and replies

Question	Assessment (<i>italicized text</i> =researcher’s assessments; <i>text without italics</i> =replies)
Requirements to report results of clinical trials	
<p>1. Does CIHR require public reporting of results from clinical trials?</p>	<ul style="list-style-type: none"> • <i>Yes, the TCPS2 (2018)¹¹⁹ requires researchers to register their CIHR-funded clinical trials and update the registry with the location of findings. CIHR does not require reporting results within the registry.</i> <p><u>Response from Secretariat on Responsible Conduct of Research:</u></p> <p>The TCPS2 is a joint policy of Canada’s three federal research agencies - the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Social Sciences and Humanities Research Council (SSHRC).</p> <p>You are correct in your assessment, that the TCPS2 does require researchers to register their clinical trials and update the registry with the location of findings.</p> <p>Article 11.10 stipulates, “all clinical trials shall be registered before recruitment of the first trial participant in a publicly accessible registry that is acceptable to the World Health Organization (WHO) or the International Committee of Medical Journal Editors (ICMJE).” Researchers are also required to provide the REB with evidence of such registration (e.g., registration number) (Article 11.10, Application).</p> <p>The TCPS2 also recognizes the importance of disseminating research findings, through publication or otherwise (Article 4.8). This includes the public reporting and updating of clinical trial registries with study research findings (Article 11.11).</p>

Question	Assessment (<i>italicized text</i> =researcher's assessments; <i>text without italics</i> =replies)
<p>1. Does CIHR require public reporting of results from clinical trials? (continued)</p>	<ul style="list-style-type: none"> • <i>According to an archived CIHR Grants and Awards Guide,²⁰⁴ researchers must report summary data from CIHR-funded clinical trials in a publicly accessible database. However, this requirement no longer applies as this policy is out of date.</i> <p>Response from Science Policy (CIHR):</p> <p>As a signatory of the WHO Joint Statement on Public Disclosure of Results from Clinical Trials, CIHR will require summary results to be publicly available within 12 months from the last visit of the last participant - note that these requirements have not yet come into effect. [Hyperlinked in original:] CIHR Signs the World Health Organization's Joint Statement on Public Disclosure of Results from Clinical Trials - CIHR (cihr-irsc.gc.ca)¹⁶⁶</p> <p>Response from the Contact Centre (CIHR):</p> <p>The CIHR Grants and Awards Guide was archived in 2019 and was replaced with the CIHR Application Administration Guide (AAG): Canadian Institutes of Health Research (CIHR) Application Administration Guide - CIHR (cihr-irsc.gc.ca) [hyperlinked in original].²⁰⁵</p> <p>Information regarding the requirement to register and publicly report clinical trial results is reflected in the TCPS2 Chapter 11 (Article 11.8 and Part D), so it was removed from the AAG. https://ethics.gc.ca/eng/tcps2-eptc2_2018_chapter11-chapitre11.html¹¹⁹</p>
<p>2. Does CIHR require public reporting of clinical trial results within a specific timeline?</p>	<ul style="list-style-type: none"> • <i>No, the TCPS2 (2018)¹¹⁹ only requires researchers to update the registry with the location of findings "in a timely manner". Similarly, it later says researchers "shall promptly update the registry." There is no specific timeline for reporting the location of results in a registry.</i> <p>Response from Science Policy (CIHR):</p> <p>As a signatory of the WHO Joint Statement on Public Disclosure of Results from Clinical Trials, CIHR will require summary results to be publicly available within 12 months from the last visit of the last participant - note that these requirements have not yet come into effect. [Hyperlinked in original:] CIHR Signs the World Health Organization's Joint Statement on Public Disclosure of Results from Clinical Trials - CIHR (cihr-irsc.gc.ca)¹⁶⁶</p>

Question	Assessment (<i>italicized text</i> =researcher's assessments; text without italics=replies)
<p>2. Does CIHR require public reporting of clinical trial results within a specific timeline? (continued)</p>	<p><u>Response from Secretariat on Responsible Conduct of Research:</u></p> <p>The TCPS2 states that researchers are responsible for disseminating research findings “in a timely manner without undue restriction” (Article 4.8). Additionally, they are responsible for updating the clinical trial registry with new information, safety (and efficacy) reports, reasons for stopping a trial early, and the location of findings (e.g. lists of publications, links to publications or to trial websites) “in a timely manner” (Article 11.11). Therefore, as you have assessed, there is “no specific timeline for reporting the location of results in a registry,” in the TCPS2.</p> <p>The TCPS2 does not have specific definitions for “in a timely manner” or “promptly”. As research varies considerably in both nature and context, the notion of “timely manner” will differ from study to study. For example, the findings of a multi-year research project with a large sample of participants, would probably take more time to be disseminated after the end of the study than the results of a short, one-time survey with fewer participants. It is up to the researcher, the institution, and the REB to determine if the proposed time frame for dissemination of the results is appropriate for the study in question.</p> <p>However, as of October 2020, CIHR has signed the World Health Organization’s <i>Joint Statement on Public Disclosure of Results from Clinical Trials</i> (“WHO Joint Statement”) [hyperlinked in original].¹⁹⁴</p> <ul style="list-style-type: none"> • <i>An archived CIHR Grants and Awards Guide²⁰⁴ indicates "grant recipients must ... if conducting a CIHR-funded randomized control trial (RCT), submit a report in the Consolidated Standards of Reporting Trials (CONSORT) format within 12 months of the end of the trial." However, this only requires submission of a report to CIHR, not a journal or trial registry, and this requirement no longer applies as this policy is out of date.</i> <p><u>Response from the Contact Centre (CIHR):</u></p> <p>The CIHR Grants and Awards Guide was archived in 2019 and was replaced with the CIHR Application Administration Guide (AAG): Canadian Institutes of Health Research (CIHR) Application Administration Guide - CIHR (cihr-irsc.gc.ca) [hyperlinked in original].²⁰⁵</p> <p>Information regarding the requirement to register and publicly report clinical trial results is reflected in the TCPS2 Chapter 11 (Article 11.8 and Part D), so it was removed from the AAG. https://ethics.gc.ca/eng/tcps2-epc2_2018_chapter11-chapitre11.html¹¹⁹</p>

Question	Assessment (<i>italicized text</i> =researcher's assessments; text without italics=replies)
<p>3. Are there any specific penalties for noncompliance with CIHR policy requiring grant recipients to publicly report the results from clinical trials (e.g., the requirement to update a registry with the location of clinical trial results)?</p>	<ul style="list-style-type: none"> • <i>No, there are no specific penalties for noncompliance with CIHR policy requiring grant recipients to publicly report the results from clinical trials. For example, the TCPS2 (2018)¹¹⁹ does not include a specific penalty for not updating a trial registry with the location of clinical trial results.</i> <p>Response from Science Policy (CIHR):</p> <p>Discussion are currently underway to determine penalties for non-compliance related to requirements of CIHR being a signatory on the WHO Joint Statement on Public Disclosure of Results from Clinical Trials. Note that these requirements have not yet come into effect.</p> <p>Response from Secretariat on Responsible Conduct of Research:</p> <p>You are correct in your assessment that the TCPS2 “does not include a specific penalty for not updating a trial registry with the location of clinical trial results.”</p> <p>TCPS2 does not contain measures for non-compliance. These are contained in the <i>Tri-Agency Framework Responsible Conduct of Research (2016)</i> (hereafter “RCR Framework”).²⁰⁶ The RCR Framework outlines the responsibilities of researchers, institutions, and the Agencies to support and promote a positive research environment. It also sets out the process to be followed when addressing allegations of breaches of Agency policies (Introduction, RCR Framework).</p> <p>Article 2.4 requires researchers to comply with all applicable Agency requirements and legislation for the conduct of research. Failure to comply with this responsibility (Article 3.1.4) or any other responsibility set out in the RCR Framework is considered a breach. Institutions are responsible for addressing allegations of breaches through an inquiry or an investigation, if warranted. If a breach is confirmed and the study is funded by CIHR, CIHR can impose a recourse against the researcher. The type of recourse that the Agency can impose depends on a number of factors including, but not limited to, the nature and severity of the breach, its impact, and whether or not the breach was committed intentionally. Examples of recourse are listed in Article 6.1.3(b).</p>

Question	Assessment (italicized text=researcher's assessments; text without italics=replies)
<p>4. If there are specific penalties for noncompliance with CIHR policy requiring grant recipients to publicly report the results from clinical trials, have any penalties ever been applied for noncompliance?</p>	<ul style="list-style-type: none"> • <i>This is an empirical question, so it could not be assessed by reviewing CIHR policy.</i> <p>This question was addressed above.</p>
<p>Guidelines for assessment of researchers</p>	
<p>5. Do CIHR guidelines for peer review specify that, when assessing applicants for funding to conduct a clinical trial (e.g., an applicant's productivity), peer reviewers should take into account the proportion of a researcher's previously funded studies that have resulted in ≥1 reports of the main results in a trial registry or peer-reviewed journal?</p>	<ul style="list-style-type: none"> • <i>No, CIHR guides and manuals for peer review^{169,207-212} do not mention taking into account the proportion of a researcher's previously funded studies that have resulted in ≥1 reports of the main results in a trial registry or peer-reviewed journal.</i> <p>Response from Science Policy (CIHR):</p> <p>As a signatory of the WHO Joint Statement on Public Disclosure of Results from Clinical Trials, CIHR will require applicants, when applying for funding, to provide the registration identifier and results to-date for all previous trials in which they were the principal investigator - note that these requirements have not yet come into effect. [Hyperlinked in original:] CIHR Signs the World Health Organization's Joint Statement on Public Disclosure of Results from Clinical Trials - CIHR (cihr-irsc.gc.ca)¹⁶⁶</p>

Question	Assessment (<i>italicized text</i> =researcher's assessments; text without italics=replies)
<p>5. Do CIHR guidelines for peer review specify that, when assessing applicants for funding to conduct a clinical trial (e.g., an applicant's productivity), peer reviewers should take into account the proportion of a researcher's previously funded studies that have resulted in ≥ 1 reports of the main results in a trial registry or peer-reviewed journal? (continued)</p>	<p>Response provided by Program Design and Delivery (CIHR):</p> <p>In the Project Peer Review manual, sections: 4.2.2.b-2 a, and d are relevant despite not specifically referencing someone applying for funding for a trial.</p> <p>Point "a" speaks to whether the applicant(s) have the appropriate expertise and experience to lead and deliver the proposed output(s), and to achieve the proposed contribution(s), as follows:</p> <ul style="list-style-type: none"> • The applicant(s) should demonstrate the combined expertise and experience needed to execute the project (i.e., deliver the proposed outputs as well as achieve the proposed contribution(s))." <p>Point "b" speaks to whether applicant adequately demonstrate productivity and progress of their research program, as follows:</p> <ul style="list-style-type: none"> • In their Summary of Progress, the applicant should: • Outline the most relevant accomplishments • Demonstrate their productivity <p>Reviewers must assess productivity broadly (i.e., not just based on publications) and consider the applicant's context (e.g., career stage, leave history). CIHR has signed the <u>San Francisco Declaration on Research Assessment</u> (DORA), which recognizes that scholarly outputs are not limited to published journal articles but can include a broader range of outputs. Reviewers are encouraged to include these in their assessments.</p> <p>Therefore, if someone is conducting trials, an important aspect of Expertise, Experience and resources criterion would be to evaluate past productivity (publications and other metrics) for similar type of research (other studies or trials). Reviewers are also asked to review the applicant(s) CV and are expected to assess the applicant(s) productivity. "Reviewers are also asked to review the applicant(s) CV(s). Through their CVs, applicants highlight their recognitions, funding history, activities and contributions that best demonstrate their leadership, significant contributions and productivity in the context of their research field(s)."</p>

Question	Assessment (italicized text=researcher's assessments; text without italics=replies)
<p>6. Do CIHR guidelines for peer review specify that, when assessing applicants for funding to conduct a clinical trial (e.g., an applicant's productivity), peer reviewers should avoid using the impact factor of journals in which a researcher has published as an indicator of research quality?</p>	<ul style="list-style-type: none"> • <i>No, CIHR guides and manuals for peer review^{169,207-212} do not explicitly instruct peer reviewers to avoid using the impact factor of journals in which a researcher has published as an indicator of research quality.</i> <p>Response provided by Program Design and Delivery (CIHR):</p> <p>The response to this question may differ. Specifically, instruction to avoid using impact factor of journals is not singled out as an approach that should be avoided. However, the manual explicitly advises reviewers that they must assess productivity broadly. In addition, it references <i>DORA</i>, which CIHR has signed and which “recognizes the need to improve the ways in which the outputs of scholarly research are evaluated, beyond the widely used journal impact factor”.</p> <p>The following paragraph outlines the instructions reviewers are expected to follow: “Reviewers must assess productivity broadly (i.e., not just based on publications) and consider the applicant’s context (e.g., career stage, leave history). CIHR has signed <u>San Francisco Declaration on Research Assessment (DORA)</u>, which recognizes that scholarly outputs are not limited to published journal articles but can include a broader range of outputs. Reviewers are encouraged to include these in their assessments” (section 4.2.2.b-2).</p>
<p>7. Do CIHR guidelines for peer review specify that, when assessing applicants for funding to conduct a clinical trial (e.g., an applicant's productivity), peer reviewers should avoid placing too much emphasis on the impact factor of journals in which a researcher has published as an indicator of research quality?</p>	<ul style="list-style-type: none"> • <i>No, CIHR guides and manuals for peer review^{169,207-212} do not explicitly instruct peer reviewers to avoid placing too much emphasis on the impact factor of journals in which a researcher has published as an indicator of research quality.</i> <p>Response provided by Program Design and Delivery (CIHR):</p> <p>In the Project Peer Review manual, specifically, there aren't any explicit instructions to avoid placing too much emphasis on journal impact factors.</p>

Question	Assessment (italicized text=researcher's assessments; text without italics=replies)
<p>7. Do CIHR guidelines for peer review specify that, when assessing applicants for funding to conduct a clinical trial (e.g., an applicant's productivity), peer reviewers should avoid placing too much emphasis on the impact factor of journals in which a researcher has published as an indicator of research quality? (continued)</p>	<ul style="list-style-type: none"> • <i>A previous CIHR Peer Review Manual for Clinician Scientist Award Applications²¹³ advised: "When assessing the quality of publications, peer review committees should focus on the quality of a publication's content and NOT simply the number of publications nor the quality or impact factor of journals." While this manual did advise peer reviewers not to place too much emphasis on the impact factor of journals in which a researcher has published, this manual is not listed in CIHR's online "Peer review: Policies and procedures"²¹² and is no longer in use.</i> • <i>The CIHR Peer Review Guide for Training and Salary Awards advises that "when assessing publications, peer review committees should focus on the quality of a publication's content."²⁰⁸ This might be contrasted with a focus on quantity or the impact factor of journals a researcher has published in, but it does not comment directly on impact factors.</i> <p><u>Response from Program Design and Delivery (CIHR):</u></p> <p>Given that the Clinician Scientist Program has sunsetted, the Clinician Scientist Reviewer Guide is no longer in use and neither is the Review Guide for Training and Salary Awards. Please also note that the question posed around peer review guidelines for "assessing applicants for funding to conduct a clinical trial" is not applicable to training awards, as we are not directly funding clinical trials through training & career support.</p> <ul style="list-style-type: none"> • <i>The Peer Review Manual - Project¹⁶⁹ highlights that CIHR has signed the San Francisco Declaration on Research Assessment (DORA). While DORA recommends not using journal impact factor as a measure of research quality in funding decisions, this manual does not explicitly comment on impact factors.</i> <p><u>Response from the Contact Center (CIHR):</u></p> <p>This point was addressed above.</p>

Question	Assessment (italicized text=researcher's assessments; text without italics=replies)
Extension period for the authority to use grant funds	
<p>8. What is the maximum extension of time that a grant recipient may be given for use of funds after the stated expiry date, for funds received to conduct a clinical trial?</p>	<ul style="list-style-type: none"> • <i>All grants receive an automatic extension for "1 fiscal year (i.e., up to March 31 of the next full fiscal year" to use funds following the stated expiry date. "Grant recipients may submit a request for an extension to the automatic extension for 1 calendar year (i.e., 12 months)" under certain circumstances.</i>¹⁷⁹ <p>Response from the Contact Center (CIHR):</p> <p>Your assessment is correct. All CIHR grants come with an automatic 1-year extension to the ATUF period unless otherwise noted in the funding opportunity or on the Authorization for Funding. In Part 3: Financial Matters of the Tri-Agency Guide on Financial Administration (TAGFA) [hyperlinked in original],¹⁷⁹ it is noted that: Grant recipients may submit a request for an extension to the automatic extension for 1 calendar year (i.e., 12 months), under the following circumstances only:</p> <p>Extended leaves of absence during the grant period Uncontrollable delays to funded research/activities</p> <p>*However, CIHR has expanded these criteria to include COVID-19 related disruptions.</p> <ul style="list-style-type: none"> • <i>At the end of the grant expiry date or extension period(s) described above, "Any residual balance remaining in the grant account must be returned to the Agency [CIHR]."</i>¹⁷⁹ <p>Response from the Contact Center (CIHR):</p> <p>This is correct. In addition, the following statement appears in the TAGFA: CIHR: Any residual balance remaining in the grant account must be returned to the Agency by means of a cheque made payable to the Receiver General for Canada.</p> <p>*However, since CIHR staff have not been able to access 160 Elgin since March 2020, due to the pandemic, we have implemented a new process through which administering institutions may return residual grant balances to CIHR via electronic transfer.</p>

Question	Assessment (<i>italicized text</i> =researcher's assessments; text without italics=replies)
<p>8. What is the maximum extension of time that a grant recipient may be given for use of funds after the stated expiry date, for funds received to conduct a clinical trial? (continued)</p>	<ul style="list-style-type: none"> • <i>In other words, following the automatic extension plus an additional extension of 1 year (if granted), any unused funds received for conducting a clinical trial would need to be returned to CIHR. Further extensions are not available to allow for using the grant funds.</i> <p>Response from the Contact Center (CIHR):</p> <p>CIHR's policies do not state that further extensions are not available following the automatic 1-year extension and the additional extension. Therefore, additional extensions to continue using grant funds may be requested provided that they are properly justified by the NPI and administering institution. An ATUF extension is an extension in time only and does not cause any financial impact.</p>

Table 6. Follow-up questions sent to the Canadian Institutes of Health Research and replies

Questions	Responses (<i>italicized text</i> =text from researcher’s questions; text without italics=replies)
<p>1. Please specify which of the following documents are relevant to assessing applicants for funding to conduct a clinical trial: ^{169,207,209-212}</p> <p>a) Canadian Institutes of Health Research. Peer Review Manual – Project [updated April 15, 2021. Accessed May 7, 2021]. Available from: https://cihr-irsc.gc.ca/e/49564.html.</p> <p>b) Canadian Institutes of Health Research. Peer Review Manual - Foundation [updated Oct 1, 2018. Accessed May 7, 2021]. Available from: https://cihr-irsc.gc.ca/e/48486.html.</p> <p>c) Canadian Institutes of Health Research. CIHR Reviewers’ Guide for New Investigator Salary Awards [updated Nov 14, 2019. Accessed May 8, 2021]. Available from: https://cihr-irsc.gc.ca/e/41208.html.</p> <p>d) Canadian Institutes of Health Research. CIHR Reviewers’ Guide for Doctoral Research Awards [updated Jul 28, 2020. Accessed May 8, 2021]. Available from: https://cihr-irsc.gc.ca/e/33043.html.</p>	<p>a) <i>Canadian Institutes of Health Research. Peer Review Manual - Project [updated April 15, 2021. Accessed May 7, 2021]. Available from: https://cihr-irsc.gc.ca/e/49564.html.</i></p> <p>This guide is used for assessing applicants for funding to conduct a clinical trial. In addition to the Project Peer Review Manual, reviewers also need to consult additional reference material - RCT evaluation criteria and headings (https://cihr-irsc.gc.ca/e/39187.html) - which addresses question 2. It should also be noted that as part of answering question 2 that for strategic competitions, we may also provide customized peer review manuals that address the particular context and evaluation criteria of those specific competitions (for e.g. innovative clinical trial FO).</p> <p>b) <i>Canadian Institutes of Health Research. Peer Review Manual - Foundation [updated Oct 1, 2018. Accessed May 7, 2021]. Available from: https://cihr-irsc.gc.ca/e/48486.html.</i></p> <p>CIHR has sunsetted this program; this guide is no longer being used.</p> <p>c) <i>Canadian Institutes of Health Research. CIHR Reviewers’ Guide for New Investigator Salary Awards [updated Nov 14, 2019. Accessed May 8, 2021]. Available from: https://cihr-irsc.gc.ca/e/41208.html.</i></p> <p>The New Investigator Salary Guide does not provide any information on reviewing Clinical trials. The purpose of the guide is to provide instructions on the peer review process for the New Investigator Salary Award competition.</p> <p>d) <i>Canadian Institutes of Health Research. CIHR Reviewers’ Guide for Doctoral Research Awards [updated Jul 28, 2020. Accessed May 8, 2021]. Available from: https://cihr-irsc.gc.ca/e/33043.html.</i></p> <p>The Doctoral Reviewer Guide does not provide any information on reviewing Clinical trials. The purpose of the guide is to provide instructions on the peer review process for the Doctoral program.</p>

Questions	Responses (italicized text=text from researcher's questions; text without italics=replies)
<p>1. Please specify which of the following documents are relevant to assessing applicants for funding to conduct a clinical trial: ^{169,207,209-212} (continued)</p> <p>e) Canadian Institutes of Health Research. CIHR Reviewers' Guide for Fellowship Awards [updated Sep 1, 2020. Accessed May 8, 2021]. Available from: https://cihr-irsc.gc.ca/e/26720.html.</p> <p>f) Canadian Institutes of Health Research. Peer review: Policies and procedures [updated Aug 22, 2017. Accessed May 8, 2021]. Available from: https://cihr-irsc.gc.ca/e/39414.html.</p>	<p>e) <i>Canadian Institutes of Health Research. CIHR Reviewers' Guide for Fellowship Awards [updated Sep 1, 2020. Accessed May 8, 2021]. Available from: https://cihr-irsc.gc.ca/e/26720.html.</i></p> <p>The Fellowship Reviewer Guide does not provide info on reviewing Clinical trials. The purpose of the guide is to provide instructions on the peer review process for the Fellowship program.</p> <p>f) <i>Canadian Institutes of Health Research. Peer review: Policies and procedures [updated Aug 22, 2017. Accessed May 8, 2021]. Available from: https://cihr-irsc.gc.ca/e/39414.html.</i></p> <p>As noted in question 1, the Project Peer Review Manual contains details about clinical trials. As well, the CIHR policy on how to integrate sex and gender into research includes a guidance document about considerations for inclusion of women in clinical trials.</p>
<p>2. Are there other CIHR peer review guides or manuals relevant to assessing applicants for funding to conduct a clinical trial, which are not included in the above list?</p>	<p>It is not possible to answer this question with 100% certainty. As noted in question 1, customized peer review manuals may also [be] used for strategic competitions. As such, the development of new guides or manuals may be underway at any time.</p>